

## **Agenda Item 11.04**

### **Post-market review of pulmonary Arterial Hypertension medicines: Further amendments to PBS restrictions for monotherapy and proposed PBS restrictions for dual combination therapy.**

#### **1 Purpose of Application**

The PBAC was requested to:

- 1.1 **Consider and accept** further revisions to the Pharmaceutical Benefits Scheme (PBS) monotherapy restrictions for PBS-listed pulmonary arterial hypertension (PAH) agents arising from discussions at the June 2019 PAH Stakeholder meeting.
- 1.2 **Consider and accept** the proposed dual combination therapy PBS restrictions for PAH agents from the endothelin receptor antagonist (ERA) and phosphodiesterase-5 inhibitor (PDE-5i) classes.
- 1.3 **Consider and comment** on the estimated cost to the PBS for extending PBS subsidy to combination therapy with ERAs and PDE-5is to patients presenting with WHO functional class (FC) III-IV symptoms.
- 1.4 **Note and consider** the price proposals received from sponsors of ERA and PDE-5i medicines for the indication of dual combination therapy for patients with WHO FC III-IV symptoms.
- 1.5 **Consider** the PBS listing of dual combination therapy with a prostanoid and a PDE-5i medicine for patients with WHO FC IV symptoms based on the evidence found under the Post-market Review of PAH medicines and requested clinical need.

#### **2 Background**

- 2.1 At the November 2018 meeting, the PBAC considered the Post-market Review (PMR) of PAH Medicines Report (Review report) and made the following recommendations to the six options presented:
  - The PBAC was of a mind to recommend the extension of PBS restrictions to patients in WHO FC II for monotherapy with targeted PAH medicines in ERA and PDE-5i medicine classes.
  - The PBAC was of a mind to recommend initial combination therapy with PBS subsidised ERA and PDE-5i medicines for patients with WHO FC III/IV symptoms with increased risk factors, and sequential combination therapy with ERA and add on PDE-5i medicine for patients with WHO FCIII/IV symptoms

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with demonstrated inadequate response to monotherapy. Accordingly, the PBAC suggested a stakeholder meeting with sponsors to progress PBS restrictions and prices for dual combination PAH therapy.

- The PBAC recommended aligning the PBS restrictions with clinical treatment guidelines by removing the current requirement to trial a vasodilator (calcium channel blocker) and by strengthening the requirement to perform right heart catheterisation for the diagnosis of PAH.
- The PBAC recommended extending the PBS restrictions to include all WHO Group 1 PAH subtypes.
- The PBAC also recommended a review of the guidelines/criteria for establishing PAH designated prescribing centres.

2.2 In March 2019, the PBAC reviewed and accepted the revised PBS restrictions for monotherapy with an ERA or PDE-5i for patients presenting in FC II, and to align PBS restrictions for PAH medicines with clinical guidelines as recommended at the November 2018 meeting.

2.3 In March 2019, the PBAC noted the Department's intent to progress a stakeholder meeting to discuss Option 3 of the PMR, i.e. potential PBS subsidised dual combination therapy (initial and/or sequential combination) with ERAs and PDE-5i medicines for patients with WHO FC III/IV PAH symptoms. PBS subsidy would be dependent on achievement of an acceptable price proposal from Sponsors of these medicines.

#### ***August 2019 PBAC meeting - removal of separate application process for PAH designated prescribing centres***

2.4 All PBS PAH monotherapy restrictions include the criterion that a 'patient must have been assessed by a physician at a designated hospital'.

2.5 At the August 2019 PBAC Special Meeting, Pharmacy Branch provided a paper on the department's existing process to manage PAH designated centres. The PBAC was informed that the application process for designated PAH hospitals is purely administrative and not supported by any legal, clinical or compliance requirements related to accessing PBS subsidised PAH medicines.

2.6 The Pharmacy Branch advised that the PAH application will be amalgamated with the on-line s94 approved hospital authority application process. The term 'designated hospital' will be removed from the PBS restrictions for PAH medicines.

#### ***PAH Stakeholder meeting***

2.7 A PAH stakeholder meeting was held on 14 June 2019 with representatives of the PAH Reference Group, sponsor companies of PAH medicines, the Department of Human Services, the Department of Health and clinicians with specific expertise in the management of PAH.

- 2.8 Participants suggested further revision of the March 2019 PBAC recommended restrictions for monotherapy with PAH medicines, namely to:
- remove the requirement to demonstrate a clinical response to treatment from the Initial 1 (new patients) and Initial 2 (change or recommencement of therapy) restrictions at 5 months; and
  - remove the requirement to provide test results for continuation at six months from the restrictions for continuing treatment (i.e. First Continuing Treatment).
- 2.9 Clinicians were of the view that they rarely cease PAH medicines when a patient's condition continues to decline, instead they add an additional therapy from a different class to the patient's regimen. It was therefore agreed that the monotherapy restrictions should be re-submitted to the PBAC with these further amendments for consideration.
- 2.10 Clinicians stated that the contemporary treatment goal for patients with PAH is to maintain or achieve low (or green) risk status in accordance with the PAH Risk Assessment in the 2015 European Society of Cardiology and European Respiratory Society (ESC/ERS) Guidelines<sup>1</sup>. Patients not reaching the clinical goals aligned with low risk are considered to have an inadequate response to treatment.
- 2.11 Reference group members from the Pulmonary Hypertension Association of Australia and New Zealand (PHSANZ) agreed to draft PBS restriction criteria that identified patients with intermediate risk (WHO FC III) symptoms and some high-risk clinical factors, as those who should be eligible for initial dual combination therapy.
- 2.12 The PHSANZ members also agreed to draft PBS restriction criteria to identify patients with WHO FC III symptoms and demonstrated inadequate response to monotherapy who would be eligible for sequential combination therapy.

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<sup>1</sup> Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeperl M. (2015). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). European Respiratory Journal. 2015;46(4):903-975.

### **3 Proposed Revised Monotherapy Restrictions**

- 3.1 The Department revised the monotherapy restrictions based on clinician's advice at the stakeholder meeting. The draft revised restrictions would remove the requirement:
- to demonstrate a clinical response to treatment from the Initial 1 (new patients) and Initial 2 (change or recommencement of therapy) restrictions at 5 months; and
  - to provide test results for continuation at six months from the restrictions for continuing treatment (i.e. First Continuing Treatment).
- 3.2 The current written Authority 'First Continuing Treatment' restriction would become redundant. The current telephone Authority 'Subsequent Continuing Treatment' restriction would become telephone Authority 'Continuing Treatment'.
- 3.3 The current Initial 2 restriction would be for change of therapy only, not for recommencement after a break and the 'balance of supply' restriction would also become redundant as further repeats could be approved by telephone under continuing therapy restriction.

*The consequences of this change would include:*

- (1) No patient would 'fail' treatment with a PAH agent for the purposes of PBS subsidy and those patients who have already 'failed' PBS subsidised treatment with particular PAH agents under existing PBS restrictions would be able to retriail the same medicine.*
  - (2) There would be no reassessment point for response to treatment and therefore no barrier to continuation of PBS subsidised therapy once patients have satisfied the criteria for initiation of treatment.*
  - (3) Criteria for access to initial PBS subsidised PAH therapy must be strong to ensure that only patients with PAH access these medicines.*
- 3.4 An overview of the proposed revised monotherapy restrictions is located in the table below.

**Table 1: Overview of further proposed changes to the PBS restrictions for PAH agents (Monotherapy)**

Restriction Treatment Phases As in current PBS Schedule	Restriction Treatment Phases Restrictions as approved by PBAC March 2019 (not implemented as yet)	Restriction Treatment Phases Draft Revised Restrictions (submit to PBAC November 2019)
Initial 1 (new patients)	Initial 1 (new patients)	Initial 1 (monotherapy - new patients)
Initial 2 (new patients)	<del>Initial 2 (new patients)</del>	<del>Initial 2 (new patients)</del>
Initial 3 (change or re-commencement of therapy for all patients)	Initial 2 <del>3</del> (change or re-commencement of therapy for all patients)	Initial 2* (monotherapy - change <del>or re-commencement of therapy for all patients</del> )
First Continuing treatment	First Continuing treatment	<del>First Continuing treatment</del>
Subsequent Continuing treatment	Subsequent Continuing treatment	<del>Subsequent</del> Continuing treatment (monotherapy)
Cessation of treatment (all patients) (bosentan only)	Cessation of treatment (all patients) (bosentan only)	Cessation of treatment (all patients) (bosentan only)
Initial 1 (new patients) or Initial 2 (new patients) or Initial 3 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply	Initial 1 (new patients) or Initial 2 <del>(new patients)</del> or Initial 3 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply	Initial 1 or Initial 2 (change <del>or re-commencement of therapy for all patients</del> ) or First Continuing treatment – Balance of supply

\*Initial 2 (monotherapy – change) has been changed from written authority to telephone authority.

## 4 Dual Combination Therapy with ERA and PDE-5i medicines

### *Proposed Dual Combination Therapy PBS Restrictions*

- 4.1 Following the stakeholder meeting the PHSANZ provided the following criteria for initial and sequential combination therapy.

#### **Initial combination therapy:**

##### One of the Major criteria

1.  $CI < 2.5$  and/or  $SvO_2 < 65\%$
2.  $RAP \geq 8$  mmHg
3. pericardial effusion
4. syncope
5. Advanced right ventricular dysfunction on echo in children who are not able to undergo cardiac catheterisation

or two Minor criteria

1. *proBNP > 300 / BNP > 50 ng/L*
2. *6MWD <440m*
3. *Signs and symptoms of RHF*
4. *Hospitalisation*
5. *Vital Signs (SBP < 110mmHg and HR > 96bpm)*
6. *eGFR <60ml/min/1.73m<sup>2</sup>*
7. *In children: Inability to undertake age appropriate activities or attend school*

**Sequential combination similar after 3 month of Mono therapy:**

Develop one or more of the Major criteria

1. *CI < 2.5 and/or SvO<sub>2</sub> < 65%*
2. *RAP > 8mmHg*
3. *pericardial effusion*
4. *syncope*
5. *Advanced right ventricular dysfunction on echo in children who are not able to undergo cardiac catheterisation*

or develop 2 of the Minor criteria

1. *proBNP > 300/ BNP > 50 ng/L*
2. *6MWD <440m*
3. *Progression of symptoms*
4. *Hospitalisation*
5. *Vital Signs (SBP < 110mmHg and HR > 96bpm)*
6. *eGFR <60ml/min/1.73m<sup>2</sup>*
7. *In children: Inability to undertake age appropriate activities or attend school*

- 4.2 The proposed criteria are very broad and, in practical terms, the qualifying criteria for initial dual combination therapy would include all patients at intermediate risk with WHO FC III symptoms. The PHSANZ also indicated a three-month review period following commencement of monotherapy was too long to leave the assessment of the need for additional of therapy.
- 4.3 In consultation with the Reference Group Chair, the Department opted to draft restrictions for dual combination therapy based on the restriction criteria from PHSANZ i.e. where patients presenting with WHO FC III or IV symptoms (essentially patients at intermediate to high risk of deterioration) could access initial combination therapy. This approach negated the requirement to have separate 'sequential combination therapy' restrictions, as there would be the ability to access combination therapy in a sequential manner through the monotherapy and initial dual combination restrictions.
- 4.4 An overview of the proposed PBS restrictions for ERA and PDE-5i PAH agents for dual combination therapy is provided in the table below.

**Table 2: Overview of the proposed PBS restriction for dual combination therapy**

<b>Draft PBS Restriction - Treatment Phase/Authority type</b>
<p><b>Initial 3 (dual combination therapy – new PBS patients)</b></p> <p><b>Authority Required (written)</b></p> <p>This treatment phase provides for:</p> <ul style="list-style-type: none"> <li>• treatment naïve patients in WHO Functional Class III-IV, or</li> <li>• patients where their PAH medicines were non PBS subsidised (i.e. compassionate access, self-funded)</li> </ul> <p>Test results from right heart catheterisation, ECHO and 6 Minute Walk Test are required to confirm diagnosis.</p>
<p><b>Initial 4 (dual combination therapy – non naïve to PBS-subsidised treatment)</b></p> <p><b>Authority Required (telephone)</b></p> <p>This treatment phase provides for:</p> <ul style="list-style-type: none"> <li>• patients who have received PBS subsidised monotherapy treatment and are now eligible for combination therapy, or</li> <li>• patients who have received combination therapy where one medicine was PBS-subsidised and the second/third medicine was not PBS-subsidised.</li> </ul>
<p><b>Initial 5 (dual combination therapy - change)</b></p> <p><b>Authority Required (telephone)</b></p> <p>This treatment provides for patients to switch medicines within the same class (endothelin receptor antagonist (ERA) class or phosphodiesterase-5 inhibitor (PDE-5i) class)</p>
<p><b>Continuing treatment (dual combination therapy)</b></p> <p><b>Authority Required (telephone)</b></p> <p>This treatment phase provides for continuing treatment for patients who have received an initial course of dual combination therapy</p>
<p><b>Cessation of treatment (all patients) (bosentan only)</b></p> <p><b>Authority Required (telephone)</b></p> <p>This treatment phase provides for patients who cease treatment with bosentan.</p>

***Feedback received from Stakeholders on Draft PBS Restrictions for PAH medicines***

- 4.5 On 26 August 2019, the Department circulated both the revised monotherapy restrictions and proposed dual combination restrictions to all attendees of the stakeholder meeting for feedback and comment. The feedback is collated in Table 1 below.

**Table 3: Feedback received on revised PBS restrictions**

Topic	Stakeholder / Reference Group	Comment
Risk status instead of WHO Functional Class	[REDACTED]	PBS restrictions for PAH medicines could be based on risk status as defined in the 2015 European Society of Cardiology and European Respiratory Society (ESC/ERS) Guidelines, instead on WHO Functional Class. WHO FC is one component of the risk status. Risk status (low, intermediate and high) would be more representative of how patients are managed in practice, of clinical management guidelines for PAH, and the goals of PAH treatment (i.e., to get patients to the low risk level).
Dual combination therapy: bosentan combined with PDE-5i	[REDACTED]	<p>Considered that dual therapy with bosentan and a PDE5i should not be included in dual combination therapy, as:</p> <ul style="list-style-type: none"> <li>clinical trial results show that the addition of a PDE5i to bosentan does not provide additional benefit in patient relevant outcomes compared with monotherapy, and</li> <li>a clinically significant drug-drug interaction has been shown to occur between bosentan and PDE5i, which reduces exposure to the PDE5i and increases exposure to bosentan. The combination would pose a quality use of medicines (QUM) and safety concerns.</li> </ul>
Medicines for combination therapy	[REDACTED]	Combination therapy with iloprost or epoprostenol with a second agent should be PBS subsidised for patients in WHO class IV or class III patients who cannot tolerate either an ERA or PDE5i.
Cautionary note for patients with left sided heart failure and preserved ejection fraction	[REDACTED]	Advised that a cautionary note advising not to use PAH medicines for patients with left sided heart failure and preserved ejection fraction (PH-HFpEF) was not required. The results of pulmonary arterial wedge pressure (PAWP) measured during right heart catheterisation would differentiate between patients with PAH and patients with PH-HFpEF.
Initial 3 Restriction: Grandfathered patients	[REDACTED]	Expressed concern that grandfathered patients may not qualify for combination therapy under the Initial 3 restriction where a patient improved WHO FC status with treatment with non-subsidised PAH medicines and the patient is currently in WHO FC II (not WHO FC III/IV)
Dual combination therapy restrictions	[REDACTED]	Supported the draft PBS restrictions for dual combination therapy.

4.6 Further revised PBS restrictions for PAH monotherapy and the proposed dual combination PBS restrictions with ERAs and PDE-5i medicines were provided to sponsors on 27 September 2019.



***Estimates of Cost to the PBS for Dual Combination Therapy with ERAs and PDE-5i medicines***

- 4.7 The Post-Market Review Section in consultation with the Pricing and Managed Access Section prepared cost estimates for combination therapy with PBS listed ERAs and PDE-5is.
- 4.8 The dispensed price/maximum quantity (DPMQ) of currently listed PAH medicines are shown in Table 4 (as at 1 October 2019):

**Table 4: Current Dispensed Price/Maximum Quantity for PBS listed PAH medicines**

<b>Name, Restriction, Manner of administration and form</b>	<b>Max. Qty</b>	<b>No. of Rpts</b>	<b>Dispensed Price for Max. Qty</b>	<b>Proprietary Name and Manufacturer</b>	
BOSENTAN 62.5MG TABLET (5618Q) 62.5MG TABLET (6429J) 1 25MG TABLET (5619R) 125MG TABLET (6430K)	1 1 1 1	0 0 0 0	\$1113.08 \$1160.47 \$1113.08 \$1160.47	Tracleer® and all other brands	Actelion and all other manufacturers
AMBRISENTAN 5 MG TABLET, 30 (5607D) 5 MG TABLET, 30 (9648T) 10 MG TABLET, 30 (5608E) 10 MG TABLET, 30 (9649W)	1 1 1 1	0 0 0 0	\$2732.65 \$2780.04 \$2732.65 \$2780.04	Volibris®	GSK
MACITENTAN 10MG TABLET (10136L) 10MG TABLET (10134J)	1 1	0 0	\$2876.47 \$2923.86	Opsumit®	Actelion

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<b>Name, Restriction, Manner of administration and form</b>	<b>Max. Qty</b>	<b>No. of Rpts</b>	<b>Dispensed Price for Max. Qty</b>	<b>Proprietary Name and Manufacturer</b>	
SILDENAFIL 20MG TABLET (9547L) 20MG TABLET (9605M)	1 1	0 0	\$254.31 \$271.87	Revatio® and all other brands	Pfizer Australia and all other sponsors
TADALAFIL 20MG TABLET (1308W) 20MG TABLET (1304P)	1 1	0 0	\$796.60 \$835.85	Adcirca®	Eli Lilly Australia
EPOPROSTENOL INJECTION 500MG 10130E INJECTION 500MG 10111E INJECTION 1.5MG 10117L INJECTION 1.5MG 10129D INJECTION & DILUENT 500MG 11090Q INJECTION & DILUENT 500MG 11069N INJECTION & DILUENT 1.5MG 11065J INJECTION & DILUENT 1.5MG 11082G	1 1 1 1 1 1 1 1	0 0 0 0 0 0 0 0	\$33.28 \$44.00 \$59.33 \$70.72 \$29.67 \$40.03 \$59.33 \$70.72	Veletri® Veletri® Veletri® Veletri® Flolan® Flolan® Flolan® Flolan®	Actelion Pharmaceuticals Australia  GlaxoSmithKline Australia
ILOPROST AMPOULE 20MG/2ML SOLUTION 5751Q 6456T	1 1	0 0	\$367.99 \$390.10	Ventavis®	Bayer Australia

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<b>Name, Restriction, Manner of administration and form</b>	<b>Max. Qty</b>	<b>Nº.of Rpts</b>	<b>Dispensed Price for Max. Qty</b>	<b>Proprietary Name and Manufacturer</b>	
RIOCIGUAT					
TABLET 500 MICROGRAM, 42, 11040C	1	0	\$1717.71	Adempas®	Bayer Australia
TABLET 500 MICROGRAM, 42, 11031N	1	0	\$1765.10		
TABLET 500 MICROGRAM, 84, 11058B	1	0	\$3482.81		
TABLET 500 MICROGRAM, 84, 11059C	1	0	\$3435.42		
TABLET 1MG, 42, 11028K	1	0	\$1765.10		
TABLET 1MG, 42, 11054T	1	0	\$1717.71		
TABLET 1MG, 84, 11053R	1	0	\$3435.42		
TABLET 1MG, 84, 11060D	1	0	\$3482.81		
TABLET 1.5MG, 42, 11046J	1	0	\$1765.10		
TABLET 1.5MG, 42, 11047K	1	0	\$1717.71		
TABLET 1.5MG, 84, 11048L	1	0	\$3435.42		
TABLET 1.5MG, 84, 11061E	1	0	\$3482.81		
TABLET 2MG, 42, 11038Y	1	0	\$1717.71		
TABLET 2MG, 42, 11045H	1	0	\$1765.10		
TABLET 2MG, 84, 11030M	1	0	\$3482.81		
TABLET 2MG, 84, 11039B	1	0	\$3435.42		
TABLET 2.5MG, 42, 11052Q	1	0	\$1765.10		
TABLET 2.5MG, 42, 11057Y	1	0	\$1717.71		
TABLET 2.5MG, 84, 11024F	1	0	\$3435.42		
TABLET 2.5MG, 84, 11035T	1	0	\$3482.81		

Source: PBS published prices

- 4.9 The following table presents a summary of PBS listed PAH medicines by line of therapy and World Health Organisation (WHO) Functional Class (FC):

**Table 5: PAH medicines by Line of Therapy and WHO Functional Class**

PAH medicines	Medicine Class	Monotherapy			Proposed Combination therapy
		WHO FC II	WHO FC III	WHO FC IV	WHO FC III-IV
Bosentan	ERA	X	X	X	X
Ambrisentan		X	X	X	X
Macitentan		X	X	X	X
Sildenafil	PDE-5i	X	X	-	X
Tadalafil		X	X	-	X
Iloprost	Prostanoid	-	X*	X	-
Epoprostenol		-	X*	X	-
Riociguat	sGC stimulator	-	X	X	-

ERA: endothelin receptor antagonist, PDE-5i: phosphodiesterase 5 inhibitor, sGC stimulator: soluble guanylate cyclase stimulator, WHO FC: World Health Organization Functional Class

\* second line treatment

### ***Sponsor Price Proposals***

- 4.10 On 27 September 2019, the Department advised sponsor companies of PAH medicines that the PBAC would likely consider the proposed PBS restrictions for combination therapy with PAH medicines at its November 2019 meeting. The proposed PBS restrictions would need to be accompanied by price proposals to ensure the ongoing cost-effectiveness of these therapies in dual combination use. Price proposals were due to the Department by 23 October 2019.
- 4.11 Three sponsors of ERA and PDE-5i medicines responded with comments and/or prices to the request for a price proposal for combination therapy.

[REDACTED]

[REDACTED]

[REDACTED]

4.12 [REDACTED] and [REDACTED] both raised concerns about combination use of bosentan and sildenafil due to:

- lack of a TGA-approved indication for bosentan in dual combination therapy,
  - clinically relevant drug-drug interactions with sildenafil and tadalafil resulting in changed pharmacokinetics of the PDE-5i and bosentan, and
  - the lack of a statistically and clinically significant benefit of bosentan in combination with sildenafil over sildenafil monotherapy (based on the primary composite endpoint from the COMPASS-2 trial).
- [REDACTED]
- [REDACTED]

4.13 Correspondence from the PHSANZ to the PBAC also raised concerns regarding the combination of bosentan and sildenafil, particularly if this were the only combination to be PBS listed. The PHSANZ considered patients intolerant of bosentan could be disadvantaged and noted that clinicians would be reluctant to switch patients to bosentan.

4.14 The PHSANZ considered that combinations with other ERAs (ambrisentan, macitentan) and a PDE-5i are preferable due to:

- the risk of hepatotoxicity associated with bosentan, and
- a higher level evidence base to support other ERA-PDE-5i combinations compared to the bosentan-sildenafil combination as is noted in international guidelines.

***Price Reductions – Statutory Price Reductions and Price Disclosure***

4.15 PBS-listed PAH medicines are subject to 5, 10, or 15-year anniversary price reductions for F1 medicines, or price disclosure for medicines in F2. Refer to Table 8 for indicated price reductions at 1 April 2020.

[REDACTED]

[REDACTED]

[REDACTED]


#### Scenarios – Cost Estimates for Dual Combination Therapy

- 4.16 Table 7 below shows internal Departmental forecasts for prescription numbers for the currently treated population with PAH WHO FC III/IV symptoms (monotherapy) until June 2023.

[REDACTED]

[REDACTED]					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

- [REDACTED]
- 4.17 The estimated cost of current monotherapy treatment for patients with WHO FCIII/IV symptoms is approximately \$75 million in 2020 increasing to \$99 million in 2024 (Table 8). ERA and PDE-5i medicines account for over 88% of this cost.

[REDACTED]

[REDACTED]					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

- [REDACTED]
- 4.18 Cost estimates were based on prescription numbers in Table 6. Cost per prescription was calculated on the published DPMQ for ERA and PDE-5i medicines (as of 1 October 2019). For the medicines in the prostanoid medicines class (weight based dosage), the average cost per script was derived from 2018 DHS data for script numbers and

benefits paid. This average cost/dispensing was also used for riociguat, (soluble guanylate cyclase (sGC) stimulator).

***Scenarios – Cost Estimates for Dual Combination Therapy***

- 4.19 The model for dual combination therapy was done using a market share approach based on the current and forecast PBS prescription numbers for PAH medicines and the current dispensed price for maximum quantity (DPMQ).
- 4.20 The model assumed that the PDE-5i medicine added to an ERA or vice versa, would reflect the current market share of these medicines within each class. That is, patients using an ERA would add either sildenafil or tadalafil in similar proportions as they are currently used in monotherapy.
- 4.21 A number of scenarios were modelled:

Scenario 1 – all PAH medicines would be listed for combination therapy at the DPMQ price. The uptake rate of combination therapy was estimated at 50% in 2020 rising to 90% in 2024 (most expensive scenario). This was based on registry data, which indicated that currently 50% of patients are using dual and triple combination therapy, where the second/third medicine is currently non-PBS subsidised.

- 4.22 Scenario 2 – the bosentan-sildenafil combination alone has been modelled using the DPMQ price. It was assumed that patients would not swap from other ERAs to bosentan to access combination therapy. Rather, incident patients would be the most likely group to initiate combination treatment with bosentan and sildenafil and therefore increase the current market share of bosentan and sildenafil over the forward estimates. The uptake rate of combination therapy was also estimated to increase, whereby 30% of patients using bosentan in monotherapy would take up combination therapy in 2020 rising to 70% in 2024 (least expensive scenario).

Scenario 3 – estimates the cost for dual combination therapy based on the sponsor's proposed price for [REDACTED] and DPMQ price for all other medicines. It assumes that all PAH medicines are listed for combination therapy with an uptake rate of combination therapy of 50% in 2020 rising to 90% in 2024.

Scenario 3a – Scenario 3a mirrors Scenario 3, but models an uptake rate of combination therapy of 40% in 2020 rising to 65% in 2024.



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[REDACTED]

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	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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[REDACTED]					

- [REDACTED]
- 4.23 The PBAC was advised that Scenario 1 and Scenario 2 provide the range of the estimated additional cost of combination therapy, from the most expensive to the least expensive.
  - 4.24 Under Scenario 1, the estimated cost to the PBS for ERA and PDE-5i medicines in combination therapy for patients in WHO FC III-IV would increase by approximately 17% in 2020 to 27% in 2024 compared to the estimated PBS cost of monotherapy with an ERA or PDE-5i medicine.
  - 4.25 Under Scenario 2, the estimated cost to the PBS would be a save of approximately 2% in 2020 rising to save of 9.5% in 2024. This cost estimate is highly sensitive to changes in the estimated market share of other ERAs moving to bosentan.
  - 4.26 Under Scenario 3, the estimated cost to the PBS would increase by approximately 11% in 2020 to 20% in 2024 compared to the estimated PBS cost of monotherapy with an ERA or PDE-5i medicine. This estimate reflects the sponsor's proposed price for [REDACTED] which also results in lower cost of monotherapy.
  - 4.27 Scenario 3a models a lower uptake of combination therapy from 40% in 2020 rising to 65% in 2024. Based on the proposed price of [REDACTED] and the DPMQ of other PAH medicines, the estimated cost to the PBS for ERA and PDE-5i medicines would increase by approximately 7.5% in 2020 increasing to 12.6% in 2024.

**Dual Combination Therapy with a Prostanoid and a PDE-5i Medicine**

- 4.28 Epoprostenol and iloprost are the only PBS listed prostanoids for the treatment of PAH in monotherapy. Epoprostenol is PBS listed for monotherapy as second line treatment for patients with WHO FC III symptoms and as first line treatment of patients with WHO FC IV symptoms. Iloprost is PBS listed as second line treatment for patients with WHO FC III symptoms except for the indication of drug and toxin induced PAH, where it may be used in first line treatment. Iloprost is also listed first line for patients with WHO FC IV symptoms.
- 4.29 Feedback from a clinician during the consultation on the restrictions for dual combination therapy highlighted the clinical need for subsidised combination therapy with a prostanoid for patients in WHO Functional Class III/IV who cannot tolerate either an ERA or PDE-5i.
- 4.30 In November 2018, in its consideration of the PMR of PAH Medicines Report, the PBAC were mindful that limiting combination therapy to the ERA and PDE-5i classes did not address clinician demand for use of a prostanoid in combination with an ERA or PDE-5i in patients in WHO FC IV (Item 9.1 PBAC November 2018 paragraph 5.4.9).
- 4.31 The findings from the systematic literature review in the Report concluded that overall in patients with PAH: the use of a PDE-5i in addition to a prostanoid relative to prostanoid monotherapy is likely to be clinically beneficial; and non-inferior to prostanoid monotherapy in terms of safety.
- 4.32 The review findings for the effectiveness and safety of dual combination therapy with prostanoids in addition to ERAs or PDE-5i in patients with PAH (WHO FC III-IV) are summarised in Table 10 below (extract from Table 7, Agenda item 9.1 PMR of PAH medicines November 2019 Ratified Minutes).

**Table 10: Summary of Evidence for Dual Combination Therapy for Patients with PAH (Table 7 from Item 9.1 PMR of PAH medicines November 2018 Ratified Minutes)**

Medicine used to Treat PAH	Clinical effectiveness trials identified	Safety trials identified	Conclusion
<b>Dual combination therapy for patients with PAH</b>			
ERA in addition to prostanoid compared with placebo plus a prostanoid	<p>Two RCTs:</p> <ul style="list-style-type: none"> <li>• BREATHE-2 enrolled treatment-naïve patients with WHO FC III/IV PAH to receive combination therapy or monotherapy.</li> <li>• Han 2017 enrolled treatment-naïve patients with WHO FC III/IV PAH to receive combination therapy or monotherapy.</li> </ul> <p>The evidence provided by these trials is summarised in Table ES.11 of the Report.</p>	<p>Two RCTs:</p> <ul style="list-style-type: none"> <li>• BREATHE-2 and Han 2017</li> </ul> <p>There were no new safety signals identified.</p> <p>The evidence provided by these trials is summarised in Table ES.12 of the Report.</p>	<p>Overall, there is uncertainty as to whether an ERA in addition to prostanoid therapy, relative to prostanoid monotherapy, is beneficial in patients with WHO FC III/IV PAH.</p> <p>Overall, although there is uncertainty, use of an ERA in addition to a prostanoid could be non-inferior to prostanoid monotherapy in terms of safety when treating patients with WHO FC III/IV PAH.</p>
PDE-5i in addition to a prostanoid compared with placebo plus a prostanoid.	<p>One RCT:</p> <ul style="list-style-type: none"> <li>• PACES-1 enrolled patients receiving long-term intravenous epoprostenol therapy to receive combination therapy with sildenafil plus epoprostenol or epoprostenol alone.</li> </ul> <p>The evidence provided by this trial for all PAH patients is summarised in Table ES.15 of the Report.</p>	<p>One RCT reported on the effectiveness of a PDE-5i in addition to prostanoid therapy in treating PAH compared with placebo plus a prostanoid:</p> <ul style="list-style-type: none"> <li>• PACES-1</li> </ul> <p>There were no new safety signals identified.</p> <p>The evidence provided by this trial is summarised in Table ES.16 of the Report.</p>	<p>Overall, the use of a PDE-5i in addition to a prostanoid, relative to prostanoid monotherapy, to treat PAH patients is likely to be beneficial.</p> <p>Overall, the use of a PDE-5i in addition to a prostanoid is likely to be non-inferior to prostanoid monotherapy in terms of safety when treating PAH patients.</p>
Prostanoid in addition to an ERA compared with a placebo plus an ERA	<p>Two RCTs:</p> <ul style="list-style-type: none"> <li>• COMBI enrolled patients with WHO FC III IPAH (who were already being treated</li> </ul>	<p>Two RCTs:</p> <ul style="list-style-type: none"> <li>• COMBI and STEP</li> </ul>	<p>Overall, there is limited evidence to suggest that the use of a prostanoid in addition to an ERA, relative to ERA</p>

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Medicine used to Treat PAH	Clinical effectiveness trials identified	Safety trials identified	Conclusion
	<p>with bosentan) to receive combination therapy with the addition of iloprost or continue bosentan monotherapy</p> <ul style="list-style-type: none"> <li>• STEP enrolled patients with PAH who were already being treated with bosentan to receive combination therapy with the addition of iloprost or continue bosentan monotherapy</li> </ul> <p>The evidence provided by these trials for patients with WHO FC III/IV PAH is summarised in Table ES.17 of the Report.</p>	<p>There were no new safety signals identified.</p> <p>The evidence provided by these trials is summarised in Table ES.18 of the Report.</p>	<p>monotherapy, in treat patients with WHO FC III/IV PAH may be beneficial. This finding would be stronger if it were replicated in additional research.</p> <p>Overall, there is considerable uncertainty as to whether the use of a prostanoid in addition to an ERA is likely to be as safe as ERA monotherapy in patients with WHO FC III/IV PAH.</p>

*Source : Extract from Table 7, Agenda item 9.1 PMR of PAH medicines November 2019 Ratified Minutes*

## **5 PBAC Outcome**

- 5.1 The PBAC considered the outcomes of the PAH stakeholder meeting, pre-PBAC responses from sponsors and correspondence from the PHSANZ regarding both the proposed additional change to monotherapy restrictions and the proposed new PBS restrictions for combination use of PDE-5i's and ERA's. The PBAC also considered the estimated cost to the PBS for dual combination therapy with ERA and PDE-5i combinations. In addition, the PBAC considered the clinical need for dual combination therapy with a prostanoid and a PDE-5i or ERA.
- 5.2 The PBAC recalled that the purpose of the PMR of PAH medicines was to address discrepancies between PBS restrictions, TGA indications and clinical guideline recommendations for the use of PAH medicines. Issues included the inclusion of PAH subtypes, PBS subsidised treatment of patients in WHO Functional Class II, and PBS subsidised combination therapy.

### ***Revised monotherapy PBS restrictions***

- 5.3 The PBAC noted that the contemporary PAH treatment goal is achievement of low risk status with pharmacotherapy<sup>2</sup>. Deterioration on monotherapy or failure to reach low risk status indicates the need to add a second PAH medicine, instead of switching medicines.
- 5.4 The PBAC also noted that under current PBS restrictions, patients are required to demonstrate response to treatment with a PAH medicine (after five months) through provision of test results to obtain continuing access to the PAH medicine.
- 5.5 The PBAC considered that removing the requirement to demonstrate response to treatment to access continuing treatment would align the PBS restrictions with clinical guideline recommendations.
- 5.6 The PBAC agreed that removal of the requirement to demonstrate response from the monotherapy restrictions would not substantially alter current clinical practice. The utilisation review of PBS PAH medicines (2017) found little evidence of patients switching between PBS PAH medicines.
- 5.7 The PBAC noted that this change would result in simplified PBS restrictions. The following restriction phases would be removed:
- First Continuing Treatment Phase, and
  - Initial 1 or Initial 2 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply.

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<sup>2</sup> Galie N et al. (2015). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *European Respiratory Journal*. 2015;46(4):903-975.

- 5.8 The PBAC recalled the March 2019 recommended changes to monotherapy restrictions strengthened the diagnostic requirement for right heart catheterisation prior to access to the first PBS subsidised treatment with a PAH medicine.

**Recommendation:**

- 5.9 **The PBAC recommended removing the requirement to demonstrate response to treatment in the current monotherapy PBS restrictions for all PAH medicines and accepted the revised monotherapy restrictions at Attachment 1.a - 1.h.**

***Dual combination therapy PBS restrictions***

- 5.10 The PBAC considered the outcomes of the June 2019 stakeholder meeting and the proposed PBS restrictions for dual combination therapy with ERA and PDE-5i medicines.
- 5.11 The PBAC acknowledged the PAH risk assessment criteria in the 2015 ESC/ERS Guidelines<sup>3</sup> and noted that the contemporary treatment goal is for patients to reach a low risk status. For those patients who do not reach low risk status on monotherapy, further medicines are added to the treatment regime to reach this goal.
- 5.12 The PBAC noted the need for objective criteria to measure risk and that the PHSANZ had put forward proposed criteria for inclusion in PBS restrictions. The PHSANZ proposed initial dual combination therapy for patients at intermediate and high risk of deterioration and sequential dual combination therapy where patients have an inadequate response after 3 months of monotherapy.
- 5.13 The PBAC noted that under the proposed PBS restrictions for combination therapy, all patients with WHO FC III-IV symptoms would be eligible to access initial dual combination therapy. The diagnostic test requirements (including right heart catheterisation) prior to access to PBS subsidised combination therapy is consistent with the PAH monotherapy restrictions. Initial treatment applications for mono or dual combination therapy should be by written authority application. Once patients have access to their first PAH medicine(s), continuing access to therapy should be by telephone authority application.
- 5.14 Based on patient registry data (2017) presented in the PMR report, approximately 50% of patients are currently using combination therapy. The PBAC considered the inclusion of grandfathering provisions were appropriate to allow access to the second medicine where it was previously not PBS subsidised. The second medicines could be either a PDE-5i added to an ERA, or an ERA added to a PDE-5i.

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<sup>3</sup> Galie N et al.(2015). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). European Respiratory Journal. 2015;46(4):903-975.

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- 5.15 The PBAC considered the modelled cost estimates of PBS subsidised PAH medicines provided by the Department and noted the ERA and PDE-5i medicines contribute approximately 88% to the total cost to the PBS of all PAH medicines in monotherapy.
- 5.16 The PBAC noted the changing trends in the market shares of PAH medicines from 2010 to 2018. Since first PBS listed in 2014, utilisation of macitentan has replaced bosentan, while the market share of other PAH medicines has remained relatively unchanged.
- 5.17 The PBAC considered that the majority of patients are currently obtaining access to dual combination therapy through multiple mechanisms, such as compassionate access programs, hospitals or privately funded. Therefore, there is little incentive for sponsors of the more expensive ERAs to provide price offers beyond offsetting the cost of PDE-5i.

*Sponsor Price Proposals*

- 5.18 The PBAC noted the sponsor responses received to the Department's request for price proposals for combination therapy.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



*Bosentan – sildenafil combination*

- 5.19 The PBAC acknowledged that, while the least expensive dual combination therapy would be the bosentan-sildenafil combination, sponsors and stakeholders expressed concern on the efficacy and safety of this combination.
- 5.20 The PBAC noted that the concerns raised by sponsors and the PHSANZ on the bosentan-sildenafil combination related to the following:
- The COMPASS-2 Trial showed no benefit of combination therapy with bosentan and sildenafil over sildenafil monotherapy (unlike other ERA/PDE-5i combinations in the SERAPHIN and AMBITION trials) based on a primary composite outcome.
  - Pharmacokinetic interactions (via CYP3A4) lead to a substantial (~73%) decrease in sildenafil exposure and mild (~20%) increase in bosentan exposure.
  - Hepatotoxicity associated with bosentan affects 5-7% of patients.
  - The bosentan – PDE-5i combinations are not as highly recommended in the 2015 ESC/ERS Guidelines.
  - Bosentan is not TGA registered for dual combination therapy, in contrast to ambrisentan + tadalafil and macitentan + PDE-5i.
- 5.21 The PBAC noted that the level of evidence for combination therapy identified in 2015 ESC/ERS Guidelines<sup>4</sup> (Table 20, Table 21) is weaker for bosentan – PDE-5i combinations compared to other combinations:
- Sequential combination therapy*
- macitentan added to sildenafil: class-level 1B
  - bosentan with PDE-5i: class-level 2B
- Initial combination therapy*
- ambrisentan and tadalafil: class-level 1B.
- 5.22 The PHSANZ registry data indicated that nearly 20% of patients on dual combination therapy used the bosentan-sildenafil combination, and 25% of patients using triple therapy used bosentan, sildenafil and epoprostenol in combination. The PBAC considered that this indicated that clinicians had managed drug-drug interactions and safety concerns.
- 5.23 The PBAC agreed with the PHSANZ that clinicians would be reluctant to change from other ERAs (macitentan and ambrisentan) to bosentan in order to access PBS subsidised combination therapy.

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<sup>4</sup> Galie N et al (2015). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). European Respiratory Journal. 2015;46(4):903-975.

- 5.24 The PBAC recalled that macitentan and ambrisentan were PBS listed on a cost minimisation basis to bosentan in monotherapy for patients with WHO FC III/IV symptoms. However, given the uncertain clinical evidence to support the equivalence of bosentan/PDE-5i combinations compared to other ERA/PDE-5i combinations, current clinical guidelines and clinician concerns over increased hepatotoxicity, the PBAC agreed that the basis for benchmarking the price of all PBS ERA/PDE-5i combinations to that of bosentan and sildenafil was not fully justified.

Cost estimates

- 5.25 The PBAC considered the estimates of cost to the PBS of extending subsidy to combination therapy with ERAs and PDE-5is to patients presenting with WHO functional class (FC) III-IV symptoms (Table 9).
- 5.26 The PBAC considered that the modelled uptake of combination therapy of 50% in 2020 increasing to 90% in 2024 (Scenarios 1 and 3) was high and that estimates in Scenario 3a were more realistic with an uptake rate for combination therapy of 40% in 2020, increasing to 65% in 2024.
- 5.27 The PBAC noted that the Scenario 3a model indicated that combination therapy would incur an additional cost to the PBS of \$64.6 million over the forward estimates (5 years). The cost of monotherapy would reduce as a result of the proposed decreased price of [REDACTED]. Overall, this would represent an increase of nearly 13% over the estimated cost of monotherapy with ERA and PDE-5i medicines in 2024 (Refer Table 9).
- 5.28 The PBAC also recalled that in considering the PMR PAH report in November 2018, it agreed, in principle, that a small incremental cost over the current PBS listed ERA/PDE-5i monotherapy market would be acceptable (Paragraph 5.4.10, Item 9.1 PMR of PAH medicines November 2018 Ratified Minutes) to allow PBS subsidised dual combination therapy for patients presenting in WHO FC III/IV.

**Recommendation:**

- 5.29 **The PBAC accepted the proposed dual combination therapy PBS restrictions for PAH medicines from the ERA and PDE-5i medicine classes, provided at Attachments 2a-2e. However, PBS listing of individual restrictions for each medicine would be subject to acceptable price offers from the sponsors of each ERA and PDE-5i medicine requesting a dual combination listing.**
- 5.30 **The PBAC recommended listing of ERAs and PDE-5s in combination where the total cost to the PBS not exceed an additional 10% over the estimated cost of monotherapy with ERAs and PDE-5i medicines (based on current DPMQs) in any one year over the forward estimates.**
- 5.31 **The PBAC did not consider that the proposals received from sponsors were sufficient to justify a recommendation for [REDACTED] or [REDACTED] to be PBS listed for dual combination therapy with a PDE-5i.**
- [REDACTED]

██████ The PBAC was also of the view that, consistent with its previous advice, the total incremental cost of combination therapy should not exceed 10% of the current PBS cost of the ERA/PDE-5i market for monotherapy, noting that financial estimates based on the assumptions in Scenario 3a (developed by the Department) present the most appropriate basis for this calculation. The PBAC requested that the Department seek a further price reduction from the sponsors of ██████ and ██████ in order to implement a listing for dual combination therapy that would not exceed this threshold.

- 5.32 The PBAC also considered that the price of tadalafil should be comparable to that of sildenafil, for tadalafil to be PBS listed for dual combination therapy.

***Prostanoid plus PDE-5i medicine combination therapy***

- 5.33 The PBAC noted the clinician input requesting dual combination therapy with a prostanoid (epoprostenol or iloprost) where patients cannot tolerate either PDE-5i or ERA medicines.
- 5.34 The PBAC noted the findings from the systematic literature review in the PMR Report that for PAH patients with WHO FC III/IV symptoms, the use of a PDE-5i in addition to a prostanoid relative to prostanoid monotherapy is likely to be clinically beneficial; and non-inferior to prostanoid monotherapy in terms of safety. The evidence was limited on use of a prostanoid in addition to an ERA, relative to ERA monotherapy.
- 5.35 The PBAC also noted that the additional cost to the PBS if sildenafil were added to a prostanoid would be small, given the low utilisation of PBS prostanoids.

**Recommendation:**

- 5.36 The PBAC was of a mind to recommend combination therapy with a prostanoid and sildenafil (or tadalafil at a comparable price) as second line treatment for patients with WHO FC III symptoms and first line treatment for patients with WHO FC IV symptoms. The PBAC requested that PBS restrictions and the estimated cost to the PBS for combination therapy with prostanoids and sildenafil be presented to the PBAC for consideration.