

**AGENDA ITEM 9.03  
POST-MARKET REVIEW OF PULMONARY ARTERIAL  
HYPERTENSION MEDICINES  
COST ESTIMATES AND PROPOSED PBS RESTRICTIONS FOR DUAL  
THERAPY WITH PROSTANOIDS AND PDE-5 INHIBITORS**

**1 Purpose**

The PBAC was requested to:

- 1.1 Consider and accept the proposed dual therapy Pharmaceutical Benefits Scheme (PBS) restrictions for pulmonary arterial hypertension (PAH) medicines from the prostanoid and phosphodiesterase type 5 inhibitor (PDE-5i) classes
- 1.2 Consider and comment on the estimated cost to the PBS of extending PBS subsidy to dual therapy with prostanoids and PDE-5i medicines.

**2 Background**

- 2.1 The PBAC first considered the Post-market Review of PAH medicines in November 2018. The PBAC considered and recommended further changes to PAH medicine monotherapy restrictions at the March 2019 and November 2019 meetings. At the November 2019 meeting, the PBAC also recommended subsidy of dual therapy and accepted PBS restrictions for the endothelin receptor antagonists (ERAs) and PDE-5i medicine classes for patients with WHO FC III/IV PAH symptoms.
- 2.2 The PBAC recommended listing of ERAs and PDE-5i medicines for dual therapy provided the total cost to the PBS would not exceed an additional [redacted] over the estimated cost of monotherapy [based on current dispensed price/maximum quantity (DPMQs)] in any one year over the forward estimates. The PBS listing of individual medicines would be subject to acceptable price reductions from sponsors.

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

- 2.3 At the same meeting (November 2019), the PBAC noted clinician input requesting dual combination therapy with a prostanoid (epoprostenol or iloprost) where patients cannot tolerate either PDE-5i or ERA medicines.
- 2.4 The PBAC recalled its November 2018 consideration of the PMR of PAH Medicines Report. At that time, it was mindful that limiting combination therapy to the ERA and PDE-5i classes did not address clinician demand for the ability to prescribe a PBS subsidised prostanoid in combination with a PBS subsidised ERA or PDE-5i medicine for PAH patients with WHO FC IV symptoms (Item 9.1 PBAC November 2018 paragraph 5.4.9).

- 2.5 The PMR systematic literature review found 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 an ERA in addition to a prostanoid, relative to prostanoid monotherapy.
- 2.6 The PBAC noted that the additional cost to the PBS if sildenafil were added to a prostanoid would be small, given the low utilisation of PBS-listed prostanoids.
- 2.7 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.

### **Monotherapy**

- 2.8 The revised PBS restrictions for all PAH medicines (monotherapy) were effective to the PBS from 1 May 2020. Access to ERAs (ambrisentan, bosentan and macitentan) and PDE-5i's (sildenafil and tadalafil) was extended to include patients with WHO FC II symptoms<sup>1</sup>. PAH patients are no longer required to demonstrate a response to initial PBS-subsidised treatment through the provision of Right Heart Catheter (RHC) composite assessment, ECHO composite assessment and 6 Minute Walk Test (6MWT) results to access continued monotherapy. Various other administrative changes were also implemented to better align PBS restrictions with clinical guidelines.

### **Dual therapy: -ERA with PDE-5i medicines**

- 2.9 [REDACTED] the sponsor of [REDACTED] approached the department to share the budget impact model for dual combination therapy with ERA and PDE-5i medicines. The Department obtained agreement from all sponsors to share the model (as it contained departmental forecasts of prescription numbers) and provided the model to interested sponsors on 21 February 2020. Sponsors seeking a PBS listing for dual combination therapy were advised to submit a pricing offer package by 20 March 2020.

### **Start - Committee-in-Confidence**

- 2.10 [REDACTED]

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<sup>1</sup> Information for Healthcare Professionals and Patients, Pharmaceutical Benefits Scheme (PBS) – Revised PBS listings for Pulmonary Arterial Hypertension Medicines, available from <http://www.pbs.gov.au/industry/listing/participants/public-release-docs/pulm-art-hypertension/PAH-fact-sheet-monotherapy-restriction-changes-1-May-2020.pdf>, accessed 13 May 2020.

2.11

**End - Committee-in-Confidence**

**Triple therapy: Prostanoid (oral) with an ERA and a PDE-5i medicine**

- 2.12 At its July 2020 meeting, the PBAC recommended the Section 85 (General Schedule) - Authority Required (delayed assessment) listing of selexipag for the treatment patients with WHO FC III or IV PAH. The recommendation for selexipag is as triple therapy in combination with an ERA and a PDE-5i.
- 2.13 The PBAC considered the claim that selexipag, when used in combination with an ERA and a PDE-5i in patients with WHO FC III and IV PAH, was superior to placebo was reasonable, but that the magnitude of the benefit was uncertain. The PBAC considered that selexipag was inferior to placebo with regards to comparative safety.
- 2.14 The PBAC had concerns regarding the modelled evaluation including clinical data limitations, uncertainty surrounding the magnitude of the clinical benefit and structural issues. The PBAC considered that given the model uncertainties, the inputs for the base case analysis should be conservative. With conservative inputs the PBAC considered the ICER to be unacceptably high, but considered this could be addressed through a price reduction for selexipag. The Committee noted that the listing of selexipag could not be finalised prior to the listing of ERA/PDE-5i dual therapy, which was recommended as part of the Post-market Review of PAH listings.

**3 Proposed Restrictions-PBS subsidised dual therapy with prostanoid and PDE-5i medicines**

- 3.1 This paper presented proposed PBS restrictions for prostanoid and PDE-5i medicine dual therapy and the modelled estimated cost to the PBS for subsidising this dual therapy.
- 3.2 Proposed PBS restrictions were circulated to Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ), Services Australia and sponsors for comment. [REDACTED] provided a Pre-PBAC response in support of prostanoid-PDE-5i dual therapy and considered the draft restrictions appropriate. Preliminary input received from Services Australia was incorporated into the draft restrictions.
- 3.3 The Department proposed the following PBS restrictions for dual therapy with a prostanoid and a PDE-5i medicine for the treatment of PAH:

**Table 1: Draft PBS restrictions: Dual Prostanoid and Phosphodiesterase Type 5 inhibitor (PDE-5i) therapy**

<b>Draft PBS Dual Prostanoid and Phosphodiesterase Type 5 inhibitor (PDE-5i) Restrictions – Treatment Phase/Authority type</b>
<p><b>Initial 1 (dual therapy – new PBS patients) - 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-IV</li> </ul> <p>Test results from right heart catheterisation, ECHO and 6 Minute Walk Test are required to confirm diagnosis.</p>
<p><b>Initial 2 (dual therapy – grandfathered patients) - Authority Required (written)</b></p> <p>This treatment phase provides for:</p> <ul style="list-style-type: none"> <li>• patients with documented WHO Functional Class III or WHO Functional Class-IV</li> <li>• patients who have received non PBS subsidised treatment with a PDE-5i and a non PBS subsidised prostanoid (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 3 (dual therapy – previously treated patients) - Authority Required (telephone/electronic)</b></p> <p>This treatment phase provides for:</p> <ul style="list-style-type: none"> <li>• patients with documented WHO Functional Class III or WHO Functional Class-IV</li> <li>• patients who have received PBS subsidised monotherapy treatment and have not achieved WHO Functional Class II status</li> <li>• patients who have not achieved WHO FC II status with PDE-5i treatment alone and are intolerant to endothelin receptor antagonist (ERA) medicines</li> </ul> <p>Test results from right heart catheterisation, ECHO and 6 Minute Walk Test must be included in the patient's medical record.</p>
<p><b>Initial 4 (dual therapy - change) - Authority Required (telephone/electronic)</b></p> <p>This treatment provides for patients to switch medicines within the same class (i.e. prostanoid class or PDE-5i class)</p>
<p><b>Continuing treatment (dual therapy) = Authority Required (telephone/electronic)</b></p> <p>This treatment phase provides for continuing treatment for patients who have received an initial course of PBS subsidised prostanoid-PDE-5i dual therapy</p>
<p><b>Cessation of treatment (all patients) (bosentan only) - Authority Required (telephone/electronic)</b></p> <p>This treatment phase provides for patients who cease treatment with bosentan.</p>

## **4 Estimates of Cost to the PBS of Dual Therapy with Prostanoid and PDE-5i medicines**

- 4.1 The dispensed price/maximum quantity of currently listed prostanoid and PDE-5i PAH medicines are shown in Table 1 (as at 1 July 2020).

**Table 2: Current Dispensed Price/Maximum Quantity for PBS listed PAH medicines**

Name, Restriction, Manner of administration and form	Max. Qty#	No. of Rpts#	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
EPOPROSTENOL INJECTION 500MG, 1 10130E INJECTION 500MG, 1 10111E INJECTION 1.5MG, 1 10117L INJECTION 1.5MG, 1 10129D ----- INJECTION AND DILUENT 500MG, 1 11090Q INJECTION AND DILUENT 500MG, 1 11069N INJECTION AND DILUENT 1.5MG, 1 11065J INJECTION AND DILUENT 1.5MG, 1 11082G	1 1 1 1 --- 1 1 1 1	0 0 0 0 --- 0 0 0 0	\$33.28 \$44.35 \$59.33 \$71.07 ----- \$29.67 \$40.38 \$59.33 \$71.07	Veletri®  Epoprostenol Sun® ----- Flolan®	Actelion Pharmaceuticals Australia Sunpharma ----- GlaxoSmithKline Australia
ILOPROST AMPOULE 20MG/2ML SOLUTION, 30 5751Q 6456T	1 1	0 0	\$349.59 \$371.31	Ventavis®	Bayer Australia
SILDENAFIL 20MG TABLET, 90 (9547L) 20MG TABLET, 90 (9605M)	1 1	0 0	\$254.31 \$272.22	Revatio® and all other brands	Pfizer Australia and all other sponsors
TADALAFIL 20MG TABLET, 56 (1308W) 20MG TABLET, 56 (1304P)	1 1	0 0	\$796.60 \$836.20	Adcirca®	Eli Lilly Australia

Source: PBS published prices 1 July 2020

# administrative changes to maximum quantities and number of repeats are expected to be effective to the PBS 1 November 2020

4.2 Table 3 below shows internal Departmental forecasts for prescription numbers for prostanoid and PDE-5i medicines for the currently treated population with PAH WHO FC III/IV symptoms (monotherapy) until 2025.

**Start - Committee-in-Confidence**



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██████████	████	████	████	████	████	████
██████████	████	████	████	████	████	████



[REDACTED]

**End - Committee-in-Confidence**

4.6 The estimated cost of monotherapy treatment for PAH patients with prostanoids and PDE-5i medicines is approximately \$ [REDACTED] in 2020 decreasing to \$ [REDACTED] million in 2025 (refer Table 5), based on the prescription costs in Table 4. Epoprostenol accounts for approximately [REDACTED] of this cost and [REDACTED] of all prescriptions.

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[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]

**End - Committee-in-Confidence**

**Cost Estimates**

4.7 Cost estimates were prepared for dual prostanoid and PDE-5i medicine therapy using a market share approach, based on the average cost per prescription for prostanoids (2019) and the DPMQ for PDE-5i medicines (1 July 2020) and the current and forecast PBS prescription numbers for these PAH medicines.

4.8 The following assumptions underpinned the estimates for prescription numbers and market share of medicines for dual therapy.

**Uptake rate**

4.9 Patient registry data from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) and the Australian Scleroderma Cohort Study (ASCS) indicate that 40% of patients are prescribed dual therapy and 10% triple therapy, with the second and third medicine sourced outside the PBS, either through compassionate access programs or privately funded. Monotherapy typically comprises ERA or a PDE-5i, dual therapy combines an ERA and a PDE-5i, and triple therapy entails the addition of a

prostanoid. This data was used to inform the modelled estimated uptake rate of dual therapy with a prostanoid and PDE-5i medicine.

- 4.10 As patient registry data indicated that prostanoid medicines are prescribed predominately in triple therapy, the following estimates assumed that current prescriptions for PBS-listed prostanoids are for patients using triple therapy who obtain the second and third medicine outside the PBS.
- 4.11 The uptake rate of add-on PDE-5i to a prostanoid was estimated to be 40-50% in 2020, rising to 80-95% of the PBS population in 2025. It was also assumed that the uptake rate of add-on prostanoid medicines to PDE-5i medicines would be very low. Registry data indicated that the majority of dual therapy included an ERA with a PDE-5i (91%). In the PHSANZ patient registry, only 1.6% of dual therapy comprised a prostanoid and a PDE-5i. No patients taking this combination were identified in the ASCS registry.
- 4.12 The PBAC was presented with a range of estimated additional costs of combination prostanoid and PDE-5i therapy. Three scenarios were modelled. Scenario 1 assumed:
- Sildenafil (at the current DPMQ) would be the only PDE-5i medicine PBS-listed for dual therapy.
  - Sildenafil would gain a higher market share of the PDE-5i market (1% of tadalafil patients would switch to sildenafil in order to access dual therapy).
  - The uptake rate of add-on sildenafil for patients receiving PBS subsidised prostanoid would increase from 50% in 2020 to 95% in 2025.
  - The uptake rate of add-on prostanoid for patients receiving PBS subsidised PDE-5i medicines would increase from 1% in 2020 to 2% in 2025.
- 4.13 Scenario 2 presented the least expensive cost estimate and assumed:
- Sildenafil (at the current DPMQ) would be the only PDE-5i medicine PBS-listed for dual therapy.
  - Sildenafil would not gain any market share from tadalafil.
  - The uptake rate of add-on sildenafil for patients receiving PBS subsidised prostanoid would increase from 40% in 2020 to 80% in 2025.
  - The uptake rate of add-on prostanoid medicines was estimated to be 1% in each year from 2020 to 2025.
- 4.14 Scenario 3 presented the most expensive cost estimate and assumed:
- Both sildenafil (at the current AEMP, \$254.31) and tadalafil ( [REDACTED] ) would PBS-list for dual therapy.
  - The market share would split [REDACTED], reflecting the current market share of these medicines. Patients using a prostanoid would add either sildenafil or tadalafil in similar proportions as currently used in monotherapy.

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- The uptake rate of add-on PDE-5i to prostanoid would increase from 50% in 2020 to 95% in 2025.
- The uptake rate of add-on prostanoid to PDE-5i would increase from 1% in 2020 to 2% in 2025.

Table 6 provided an estimate of the additional prescriptions for dual therapy for each scenario. Additional prescriptions were estimated to range from [REDACTED] prescriptions in 2020, increasing to [REDACTED] prescriptions in 2025. The majority of additional prescriptions were for PDE-5i medicines.

**Start - Committee-in-Confidence**

[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]
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	[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]

End - Committee-in-Confidence

## 5 Estimates of Cost to the PBS of Dual Therapy with Prostanoid and PDE-5i medicines

- 5.1 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. The PBAC’s November 2018 consideration of the PMR Report resulted in recommendations for amendments to PBS PAH medicine monotherapy restrictions to address these issues. These included alignment of the PAH definition with clinical guidelines, strengthening the role of right heart catheterisation in diagnosis, removal of the requirement to trial a vasodilator, inclusion of all Group 1 PAH subtypes, removal of the requirement to demonstrate response to access continued treatment and extension of PBS subsidised monotherapy with endothelin receptor antagonist (ERA) and PDE-5i medicines to PAH patients with WHO Functional Class II symptoms. These changes were effective to the PBS 1 May 2020.
- 5.2 The PBAC also recalled its November 2019 recommendation for PBS subsidised dual therapy (ERA and PDE-5i) for patients with WHO FC III-IV symptoms. Progression to PBS-listing was subject to receipt of acceptable price offers from medicine sponsors. The PBAC noted the Department’s advice that acceptable price offers had been received and PBS-listing of this dual therapy (bosentan, macitentan, sildenafil, tadalafil) was expected to be effective from 1 October 2020.
- 5.3 The PBAC acknowledged that the PMR of PAH looked extensively at the evidence base for the use of PAH medicines. The PMR found that for 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 more limited on use of a prostanoid

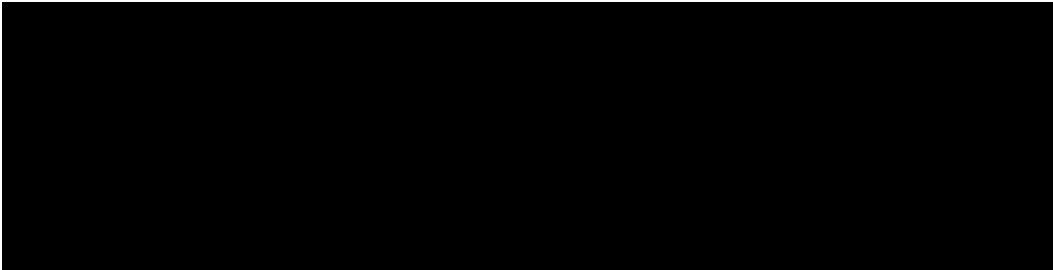
in addition to an ERA, relative to ERA monotherapy (refer Table 7, Agenda item 9.1 PMR of PAH medicines November 2019 Ratified Minutes).

- 5.4 The PBAC noted an analysis of the PHSANZ registry data demonstrated that ERA- PDE- 5i dual therapy was the preferred dual therapy for 91% of PAH patients, 3.2% of patients used the prostanoid-PDE-5i combination and the proportion of patients using prostanoid-PDE-5i dual therapy was 1.6%, but likely to change.
- 5.5 The PBAC acknowledged that PBS listing of ERA-PDE-5i dual therapy and potential listing of prostanoid-PDE-5 dual therapy would not provide a PBS subsidised dual therapy option for those PAH patients who cannot tolerate or have contraindications to either a PDE-5i (and can't use either combination) or ERA medicine (and can't use the ERA-PDE-5i combination). The PBAC recalled its recent (July 2020) recommendation to list selexipag (an oral prostacyclin receptor agonist) as triple therapy in combination with an ERA and a PDE-5i medicine for PAH patients with WHO FC III or IV symptoms who have not achieved WHO FC II with dual therapy. The PBAC considered potential PBS listing of ERA-prostanoid dual therapy would provide PAH patients the opportunity to access another treatment option, consistent with current PAH clinical treatment guidelines.
- 5.6 Accordingly, the PBAC requested that the Department present PBS restrictions and the estimated cost to the PBS for dual therapy with a prostanoid (iloprost and epoprostenol) and ERA second line for patients with WHO FC III symptoms and first line for patients with WHO FC IV symptoms for future consideration.

**Committee in confidence**

5.7 

5.8 

5.9 

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- 5.10 The PBAC also noted [REDACTED] provided a pre-PBAC response in support of PBS-subsidised prostanoid-PDE-5i dual therapy and the proposed PBS restrictions.
- 5.11 Given the low utilisation of PBS subsidised prostanoids, the PBAC accepted the incremental cost of extending PBS subsidy to dual therapy with PDE-5i (sildenafil and tadalafil) and prostanoid (epoprostenol and iloprost) medicines for second line treatment for PAH patients with WHO FC III symptoms and first line treatment for PAH patients with WHO FC IV symptoms.
- 5.12 In making this recommendation, the PBAC considered the potential effect of the recommended listing for selexipag was uncertain. Selexipag was highly likely to replace some inhaled and intravenous prostanoid use, particularly for those PAH patients with WHO FC III symptoms. The PBAC also considered increased uptake of PBS subsidised PDE-5i and prostanoid dual therapy was likely to occur.
- 5.13 The PBAC accepted the proposed dual therapy PBS restrictions for prostanoid and PDE-5i medicines in principle, noting that due to the complexity the restrictions were to be finalised out of session.