Agenda item 9.03

Medicine utilisation and cost analysis of Pharmaceutical Benefits Scheme listed medicines for pulmonary arterial hypertension (PAH)

1 Purpose

That the PBAC:

1.1 **Consider** the findings of the 'Medicine utilisation and cost analysis of Pharmaceutical Benefits Scheme (PBS) listed medicines for pulmonary arterial hypertension (PAH)' report, including the contemporary doses of prostanoid medicines and the estimated cost to the PBS of listing endothelin receptor antagonist (ERA) + prostanoid dual therapy.

1.2 **Note** the findings of the cross-sectional analysis of patient registry data (Dec 2021) by medicine and World Health Organisation (WHO) Functional Class (FC) provided by the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ).

1.3 **Consider** the February 2022 Drug Utilisation Sub-Committee (DUSC) advice for this item.

1.4 **Consider and make recommendations** on the PBS listing and proposed restrictions for ERA + prostanoid dual therapy for PAH patients with WHO FC III and WHO FC IV symptoms.

1.5 Consistent with DUSC February 2022 advice and a request from PHSANZ, **consider and make recommendations on** the PBS listing of ERA + phosphodiesterase-5 inhibitor (PDE-5i) + prostanoid triple therapy for PAH patients with WHO FC IV symptoms.

1.6 **Note** the sponsor Pre-Sub-Committee Responses (PSCRs) and Pre-PBAC responses.

2 Background

2.1 In September 2020, the PBAC requested that the Department present proposed PBS restrictions and the estimated cost to the PBS of subsidising prostanoid (iloprost and epoprostenol) and ERA dual therapy, second line for patients with WHO FC III symptoms and first line for patients with WHO FC IV symptoms.

2.2 The Department commissioned an independent contractor, [redacted] to undertake a medicines utilisation and cost analysis of PBS listed medicines for PAH, with a focus on prostanoid medicines. Patient level data for all prescriptions for medicines listed for PAH dispensed between 1 January 2010 and 31 December 2020 were analysed. Selexipag (PBS listed 1 February 2021) was not included in the analysis.

2.3 In November 2021, the Department engaged PHSANZ to provide clinical advice on treatment pathways and an updated analysis of its patient registry data, previously analysed in 2018 to inform the PMR of PAH medicines. The PHSANZ registry captures medicine use that is funded via the PBS, privately or through compassionate programs.

2.4 The PHSANZ provided:

- A cross-sectional analysis of the PHSANZ registry data on alive patients including clinical characteristics and functional status at the time of diagnosis.
- Patterns of PAH medicine use, including combination therapy in real world clinical practice with associated functional class at last recorded follow-up.
- Epoprostenol doses for patients using epoprostenol under the care of the six major PAH centres in Australia.

2.5 The clinical input from PHSANZ was used to reduce the uncertainty around contemporary treatment pathways and to further inform the assumptions used to model the financial estimates.

3 Key findings

Medicine utilisation analysis 2010-2020

3.1 The medicine utilisation analysis found:

- The annual number of dispensings for medicines to treat PAH increased from [redacted] in 2010 to [redacted] in 2020. The corresponding PBS benefit paid increased from $44.1 million to $70.5 million (published prices) over the same period.
- ERAs were the most dispensed medicine class, accounting for 80% of all PAH dispensings in 2020.
- Macitentan was the most dispensed PAH medicine after 2016.
- The annual number of treated patients increased from [redacted] in 2010 to [redacted] in 2020, with the majority being women (73% in 2020).
- Incident patients (new to use of medicines for PAH) remained relatively stable across the period, with [redacted] people incident users in 2020. The mean age was similar between females and males (65 years in 2020).

- For iloprost, the median dose increased from 15mcg at initiation to 23mcg at year 1,2 and 3 post initiation based on 2.5mcg per inhale. The median dose increased from 30mcg at initiation to 45mcg at year 1,2 and 3 post initiation based on 5mcg per inhale.

- For epopostenol, the median dose started at 16 ng/kg/min over the first three months and escalated in steps to 35 ng/kg/min at 36 months.

PHSANZ patient registry analysis

3.2 Based on the analysis conducted in December 2021, PHSANZ advised:

- Most patients (58.4%) were on either dual or triple combination therapy and this result was slightly higher than the 49.7% on combination therapy reported in the 2018 analysis of PAH registry data.
- Of the [redacted] registry patients with FC status recorded, 51.2% did not reach low risk FC I or FC II status despite modern pharmacotherapy. These results are consistent with reports from other international registries.
- Overall, prostanoids were used by [redacted](5.5%) of patients, with [redacted] patients using prostanoids as part of triple therapy. PHSANZ advised this is consistent with current treatment guidelines that recommend patients at high risk of early mortality be offered triple therapy including parenteral prostanoids.
- The majority (47.8%) of patients on treatment remain in FC III status. The most common therapy in this group was the ERA + PDE-5i combination.
- The therapeutic options for patients remaining in FC III despite treatment with the ERA/PDE-5i combination include: (a) adding selexipag (triple oral combination), (b) switching to prostanoid-PDE-5i combination whilst accessing ERA therapy outside of the PBS or (c) continuation of ERA/PDE-5i dual therapy if escalation of therapy was considered inappropriate.
- Less than 10% of patients with PAH are FC IV at the time of diagnosis. Some patients who are currently eligible for initial treatment with a PBS prostanoid will choose not to commence this medicine for a variety of reasons.
- Only 3.5% of patients with PAH used epoprostenol as part of their treatment regimen. Despite FC III/IV status, low utilisation of epoprostenol may be due to: limited access to PAH centres with expertise in administering epoprostenol, the impact on lifestyle of medicine delivery via portable infusion pump/indwelling central line and patient co-morbidities/intolerance to intravenous epoprostenol.
- High rates of ERA and PDE-5i monotherapy use persists in patients with PAH FC III or IV symptoms due to advanced age, co-morbidities, or intolerances to other classes of PAH medicines.
- The mean dose of epoprostenol from a survey of patients treated at six major Australian PAH centres was 29.8 ng/kg/min.
- Currently 87.3% of patients using epoprostenol receive ERAs via compassionate access schemes.
- [redacted]patients from the six major centres were taking selexipag as part of triple oral therapy, of these 43.4 % were in FC III, the remainder in FC I or II. Selexipag does not replace epoprostenol for patients in FC IV, however triple oral therapy may be the 'destination' triple therapy for a proportion of patients with severe PAH.
- Should the ERA + prostanoid combination be subsidised, PHSANZ considered a major change in prostanoid utilisation unlikely and that PBS utilisation of ERAs may increase slightly, as patients accessed the ERA from the PBS rather than from non-PBS sources.

Financial Estimates 2021-2026

3.3 The 2021 analysis of the PHSANZ patient registry data showed that among all people with PAH in the registry, 10% had WHO FC I symptoms, 39% had FC II, 48% had FC III and 3% had FC IV symptoms.

3.4 A market share approach was used to estimate the cost to the RPBS/PBS, based on PHSANZ registry data. The subsidised and non-subsidised use of pharmacotherapies for people with PAH, showed that 42% of patients were on monotherapy and 58% were on combination therapy (either dual or triple).

3.5 It was estimated that by 2026, under the current PBS listings for PAH medicines, there will be [redacted] people who will receive [redacted] prescriptions for ERA, prostanoid, PDE-5i or selexipag medicines at a cost of [redacted] (at published prices) to the PBS.

Table 1: Estimated total expenditure to the PBS excluding co-payment (at published prices) for PAH medicines under current PBS listings, 2022-26

Year	2022	2023	2024	2025	2026	Total
Net Cost ($ millions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.6 It was estimated that by 2026, if ERA + prostanoid dual therapy is PBS subsidised, the additional cost to the PBS is estimated to be $[redacted] over the five years 2022-26.

Table 2: Estimated total additional PBS expenditure excluding co-payment (at published prices) for ERA + prostanoid dual therapy, 2022-26

Year	2022	2023	2024	2025	2026	Total
Net Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 3: Estimated total additional PBS expenditure excluding co-payment (at effective prices) for the ERA + prostanoid dual therapy, 2022-26

Year	2022	2023	2024	2025	2026	Total
Net Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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3.7 The PBAC was aware that should ERA + prostanoid dual therapy be subsidised, triple therapy (ERA + PDE-5i + inhaled/IV prostanoid) would be the only outstanding treatment regimen for PAH patients not PBS subsidised. PHSANZ advised triple therapy is required by a small number of patients (less than 5.5% of registry patients)[1] late in their disease and clinical guidelines recommend treatment for all WHO FC stages of PAH, for any PAH subtype with any medicine or combination of medicines.

[1] Cross-sectional analysis of patient registry data (Dec 2021) by medicine and WHO Functional Class FC provided by the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) p.11

3.8 The estimated additional cost to the PBS for the triple therapy combination (ERA + PDE-5i + inhaled/intravenous prostanoid) for patients with WHO FC IV symptoms was estimated to be [redacted] (at published prices) for the five years 2022-2026. This represents only a small increment of approximately [redacted] to fund the PDE-5i component of triple combination therapy over the forward estimates.

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Table 4: Estimated total additional cost to the PBS for the ERA + PDE-5i + prostanoid combination excluding co-payment (at effective prices), 2022-2026.

Year	2022	2023	2024	2025	2026	Total
Cost PDE-5i	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 5: Estimated total additional cost to the PBS for the ERA + PDE-5i + prostanoid combination excluding co-payment (at published prices), 2022-2026.

Year	2022	2023	2024	2025	2026	Total
Cost PDE-5i	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4 PBAC Outcome

4.1 Following consideration of the Post-Market Review of pulmonary arterial hypertension (PAH) medicines, the PBAC recalled it had requested that the department prepare revised PBS restrictions and costs to the PBS for endothelin receptor antagonist (ERA) and prostanoids in dual therapy for patients with PAH, second line for patients with WHO FC III symptoms and first line for patients with WHO FC IV symptoms.

4.2 The PBAC considered the findings of the 'Medicine utilisation and cost analysis of Pharmaceutical Benefits Scheme (PBS) listed medicines for PAH' report, the December 2021 cross-sectional analysis of the PHSANZ patient registry data, proposed PBS restrictions for dual ERA + prostanoid therapy, February 2022 DUSC advice and the sponsors' pre- subcommittee and pre-PBAC responses.

4.3 Overall, the PBAC accepted the key findings presented in the medicine utilisation and cost analysis and the patient registry analysis.

4.4 The PAH incident patient population is stable, and the prevalent patient population is growing. The PBAC noted that the increase in prevalent PBS population may be due to patients with PAH surviving longer on treatment, treatment with PAH medicines earlier in the disease and/or improved tolerability to treatment.

4.5 The PBAC noted [redacted] provided PSCRs and pre-PBAC responses. [redacted] sponsors were generally supportive of the key findings, the proposal for PBS-subsidised access to ERA + prostanoid dual therapy and the suggestion from DUSC that

the PBAC may wish to consider subsidy of ERA + prostanoid + PDE-5i triple therapy for patients with WHO FC IV symptoms requiring access to inhaled or intravenous prostanoids as part of triple therapy. [redacted] was disappointed that its request to subsidise [redacted] therapy was considered beyond the scope of this item.

4.6 The PBAC also noted implementation of its recommendations made under the Post-market Review of PAH medicines has resulted in improved access to subsidised medicines for patients with PAH. Monotherapy with ERA and PDE-5i medicines was extended to patients with WHO FC II symptoms and access to subsidised dual therapies (ERA + PDE-5i, PDE-5i + prostanoid) was made available for patients with WHO FC III/IV symptoms. Separate to outcomes of the PMR, the PBAC recalled that selexipag (an oral prostacyclin agonist) was PBS listed on 1 February 2021 for dual and triple oral therapy in combination with an ERA and/or a PDE-5i for PAH patients with WHO FC III/IV symptoms.

4.7 The PBAC noted DUSC advice that subsidising the ERA + prostanoid combination first line for patients with WHO FC IV symptoms and second line for patients with WHO FC III symptoms was unlikely to cause a major change in PBS prostanoid utilisation. DUSC considered PBS utilisation of PDE-5i medicines may decrease slightly and that there may be a small increase in PBS utilisation of ERAs.

4.8 The PBAC also noted the DUSC advice and PHSANZ input that subsidy of ERA + prostanoid dual therapy will likely result in those patients currently using ERA + PDE-5i + prostanoid triple therapy shifting from PBS subsidised PDE-5i + PBS prostanoid (and receiving the ERA via non-PBS sources) to PBS subsidised ERA + PBS subsidised prostanoid. The PDE-5i would then be accessed via a non-PBS source. DUSC was concerned that this could lead to potential inequities in access to PDE-5i medicines for these patients.

4.9 The PBAC recalled stakeholder input to the PMR that highlighted that the financial burden and uncertainty associated with guaranteeing the continued availability of PAH targeted medicines through non-PBS avenues is a cause of stress and anxiety for consumers.

4.10 The PBAC noted PHSANZ's request for PBS subsidy of triple therapy including prostanoids (inhaled or intravenous) for the small group of patients with severe PAH (WHO FC IV) who are at high risk of early mortality, given current treatment guidelines[2,3] recommend that these patients should be offered this combination.

4.11 Clinical guidelines suggest the overall treatment goal for patients with PAH is to achieve low risk status (usually WHO FC II). For patients stabilised on monotherapy yet

[2]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): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT).
[3]Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report (American College of Chest Physicians, 2014)

not meeting treatment goals, guidelines support the addition of another medicine from a different therapeutic class (ERAs, PDE-5 inhibitors, prostanoids), up to a maximum of three PAH targeted medicines, rather than changing to monotherapy from a different therapeutic class.

4.12 The PBAC noted DUSC's suggestion that it may wish to consider subsidy of this triple therapy to improve access and mitigate potential inequities to treatment for patients with severe (FC lV) PAH, and for consistency with current clinical guidelines. The DUSC noted the additional cost of subsidising the PDE-5i for this group of patients is less than $1 million per year and would have only a small effect on the overall net cost to the PBS.

4.13 The PBAC noted that DUSC considered that the assumptions used in the modelling were reasonable and that the cost estimates for subsidising ERA+ prostanoid would be at the upper limit of the estimated additional PBS expenditure. The modelling may have underestimated the triple oral therapy market (selexipag + ERA+ PDE-5i) that substitutes triple therapy that includes an intravenous or inhaled prostanoid. The PBAC considered that the additional cost to the PBS of subsidising the ERA + intravenous or inhaled prostanoid combination will be lower than [redacted] over the five years 2022-26.

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4.14 [redacted]

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4.15 The PBAC noted that the actual selexipag PBS utilisation data [redacted] immature given its recent PBS listing. The PBAC considered that the uptake of selexipag based on dual or triple therapy was likely to increase for patients with WHO FC III symptoms. The PBAC also noted that, although selexipag does not replace epoprostenol therapy for patients with PAH in WHO FC IV, triple oral therapy may be the 'destination' therapy for a proportion of patients with severe PAH.

4.16 The PBAC noted that inhaled iloprost has a place in PAH therapy, however utilisation of iloprost is decreasing and oral selexipag is increasingly preferred by clinicians. The PBAC considered the extent to which triple oral therapy may displace, delay or

substitute ERA + PDE-5i + inhaled/intravenous prostanoid therapy in the future is unknown. However, the PBAC considered that increased selexipag use and substitution of a proportion of the inhaled and intravenous prostanoid market was likely to be higher than that modelled in the report and may reduce the cost to the PBS for ERA + inhaled and intravenous prostanoids over the forward estimates.

4.17 The PBAC recommended the subsidy of ERA + prostanoid dual therapy, first line for patients with PAH with WHO FC IV symptoms and second line for patients with PAH with WHO FC III symptoms. The PBAC considered that the estimated total additional PBS expenditure for ERA + prostanoid dual therapy of [redacted] over the five years 2022-26 was likely at the upper limit of the additional PBS expenditure modelled. The PBAC noted that Grandfather patients had been included in the financial estimates. The PBAC requested that revised estimates be prepared closer to the time of implementation on the PBS. The modelled assumptions should include actual use of selexipag informed by PBS utilisation data and the previously department-sponsor agreed uptake rates.

4.18 The PBAC also recommended the listing of ERA + inhaled/intravenous prostanoid + PDE-5i triple therapy for patients with PAH WHO FC IV symptoms, based on DUSC advice that the small additional cost of less than $[redacted] to the PBS would address current inequities in access and further align PBS restrictions with contemporary clinical guidelines.

4.19 The PBAC accepted the proposed ERA + prostanoid dual PBS restrictions, noting that flow on changes to ERA, prostanoid and PDE-5i medicine PBS restrictions, including grandfather restrictions, will be required to implement the recommendation as intended for ERA + inhaled/intravenous prostanoid + PDE-5i triple therapy.

Outcome:
Recommended