Changes have been made to this public summary document. Details of the corrigendum are at the end of this document.

5.14 MACITENTAN WITH TADALAFIL, Tablet containing macitentan 10 mg with tadalafil 40 mg, Opsynvi®, JANSSEN-CILAG PTY LTD.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Highly Specialised Drug Program) Authority Required (Written) listing for macitentan 10 mg with tadalafil 40 mg (Opsynvi®, herein referred to as MAC+TAD) fixed dose combination (FDC) for the continuing treatment of pulmonary arterial hypertension (PAH) in patients who are on stable doses of macitentan and tadalafil as combination therapy.

1.2 Listing was requested on the basis of a cost-minimisation approach versus separate doses of macitentan 10 mg tablets with 2 x 20 mg tadalafil tablets as dual therapy or with a prostanoid as triple therapy.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with WHO functional class (FC) III and IV pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) who are on stable, separate doses of macitentan 10 mg and tadalafil 40 mg (20 mg x 2).
Intervention	Macitentan 10 mg with tadalafil 40 mg (Opsynvi®) fixed dose combination (FDC) daily, as dual therapy or with a prostanoid or selexipag as triple therapy.
Comparator	Macitentan 10 mg tablet with 2 x 20 mg tadalafil tablets as dual therapy or with a prostanoid as triple therapy.
Outcomes	Simplify dosing regimen; reduce pill burden for patients.
Clinical claim	In adults with PAH, MAC+TAD FDC is bioequivalent to separate doses of macitentan 10 mg and tadalafil 40 mg (20 mg x 2 tablets).

Source: Compiled during the evaluation. Abbreviations: MAC+TAD = macitentan 10 mg with tadalafil 40 mg (Opsynvi®) fixed dose combination (FDC); PAH = pulmonary arterial hypertension.

2 Background

Registration status

2.1 MAC+TAD FDC was registered by the Therapeutic Goods Administration (TGA) on 16 September 2024 on the basis of it being bioequivalent to treatment with one macitentan 10 mg tablet and two 20 mg tadalafil tablets.

2.2 MAC+TAD FDC is indicated for the maintenance treatment of pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) in adult patients of

WHO functional class (FC) II and III whose PAH is idiopathic, heritable or associated with connective tissue disease or congenital heart disease with repaired shunts.

2.3 The Advisory Committee on Medicines (ACM) noted that efficacy data was not provided in the TGA submission to support the use of MAC+TAD FDC in the treatment of functional class IV PAH patients. The ACM advised that while, in practice, many class IV patients are treated with tadalafil and that it is likely that this will continue to be the case with this FDC, this is not a sufficient basis to support registration of this indication in class IV patients. The ACM agreed with the TGA Delegate that restriction of the indication to class II and III patients in line with the US and Canada was appropriate. The TGA Delegate noted that the sponsor had highlighted current practice and international guidelines as supporting its use in FC IV.

2.4 Table 2 provides a summary of the different indications approved by TGA, PBS and other international regulation or reimbursement agencies.

Table 2: Comparison of MAC+TAD FDC, macitentan and tadalafil indications for TGA, PBS and international regulators

Medicine	Therapy	TGA	PBS	International		
				FDA	EMA	CDA
MAC+TAD FDC	Combination	PAH WHO Group 1, FC II and III	Not yet PBS-listed (Proposed indication – PAH WHO Group 1, FC III and IV)	PAH WHO Group 1, FC II and III	PAH WHO Group 1, FC II and III	PAH WHO Group 1, FC II and III
MAC	Monotherapy	PAH WHO FC II, III and IV	PAH WHO FC II, III and IV	PAH WHO Group 1, FC not specified[a]	PAH WHO FC II and III	PAH WHO Group 1, FC II and III
	Combination with TAD	PAH WHO FC II, III and IV	PAH WHO FC III and IV	Not specified	Not specified	PAH WHO Group 1, FC II and III
TAD	Monotherapy	PAH WHO FC II and III	PAH WHO FC II and III	PAH WHO Group 1, FC not specified[a]	PAH WHO FC II and III	PAH WHO Group 1, FC II and III
	Combination with MAC	Not specified	PAH WHO FC III and IV	Not specified	Not specified	Not specified

Compiled during the evaluation. Sources: ACM minutes August 2024 meeting, TGA website[1], PBS website, FDA website[2], EMA website[3], CDA website[4] (formerly CADTH). Abbreviations: CDA = Canada's Drug Agency (formerly CADTH); EMA = European Medicines Agency; FC = functional class; FDA = United States' Food and Drug Administration; FDC = fixed dose combination; MAC = macitentan; PAH = Pulmonary Arterial Hypertension; PBS = Pharmaceutical Benefits Scheme; TAD = tadalafil; TGA = Therapeutic Goods Administration; WHO = World Health Organisation.

Note: Switzerland's registration information was not included as the MAC+TAD FDC indication is not yet available.

[a] FDA indications note that FC II and III are the main functional classes that the medicines have established effectiveness in.

Previous PBAC consideration

2.5 MAC+TAD FDC has not been previously considered by the PBAC.

2.6 Macitentan was recommended for the treatment of PAH by the PBAC at its March 2014 meeting and has been listed since September 2014.

[1] Public Summary for 172882 ADCIRCA tadalafil 20mg tablet blister pack, Therapeutic Goods Administration (TGA), effective 22/05/2024, accessed via https://www.tga.gov.au/resources/artg/172882; Public Summary for 205624 OPSUMIT macitentan 10 mg film coated tablet blister pack, TGA, effective 24/06/2024, accessed via https://www.tga.gov.au/resources/artg/205624

[2] Label for SUPPL-24 for New Drug Application (NDA) 204410, OPSUMIT, MACITENTAN, 10MG, Food and Drug Administration (FDA), effective 26/05/2023, accessed via https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=204410; Label for SUPPL-11 for New Drug Application (NDA) 022332, ADCIRCA, TADALAFIL, 20MG, FDA, effective 15/09/2020, accessed via https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022332

[3] Opsumit: macitentan, European Medicines Agency (EMA), last updated 06/12/2023, https://www.ema.europa.eu/en/medicines/human/EPAR/opsumit; Adcirca (previously Tadalafil Lilly): tadalafil, EMA, last updated 09/07/2024, https://www.ema.europa.eu/en/medicines/human/EPAR/adcirca-previously-tadalafil-lilly

[4] Macitentan Recommendation and Reasons Report, 28/01/2015, Canada's Drug Agency (CDA), accessed via: https://www.cda-amc.ca/macitentan; Tadalafil Recommendation and Reasons Report, 15/07/2010, CDA, accessed via https://www.cda-amc.ca/tadalafil

2.7 Tadalafil was recommended for the treatment of PAH by the PBAC at its November 2011 meeting and has been listed since April 2012. Since this time, additional brands of tadalafil have been listed on the PBS.

2.8 As part of the post-market review of PAH medicines minutes, (PBAC Meeting, November 2018) the PBAC recommended the extension of PBS subsidised access to combination therapy with various combinations of endothelin receptor agonists (ERA) and phosphodiesterase-5 inhibitors (PDE-5i), soluble guanylyl cyclase (sGC) stimulator and prostanoids for patients with PAH in WHO FC III-IV. This included the recommendation of combination therapy of macitentan 10 mg and tadalafil 2 x 20 mg for the treatment of patients with WHO FC III or IV PAH.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 The submission requested the following new listing. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
MACITENTAN + TADALAFIL						
macitentan 10 mg + tadalafil 40 mg tablet, ~~oral~~ *30*		NEW	1	30	5	Opsynvi
Restriction Summary [new] / Treatment of Concept: [new]						
	Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
	Prescriber type: ☒Medical Practitioners					
	Restriction type: ☒Authority Required (~~Written~~ *Telephone/online PBS Authorities system*)					
	Authority type: ☒ Complex Authority Required (CAR)					
	Indication: Pulmonary arterial hypertension (PAH)					
	Treatment Phase: Continuing treatment ~~–~~*of* combination therapy (dual or triple therapy, excluding selexipag)					
	Clinical criteria:					
	The treatment must ~~form~~ be dual combination therapy as a fixed dose combination consisting of*: (i)* macitentan ~~and~~ *(ii)* tadalafil; or					
	The treatment must ~~form~~ be part of triple combination therapy as a fixed dose combination consisting of*: (i)* macitentan, *(ii)* tadalafil ~~and~~ *(iii)* one prostanoid.					
	Treatment criteria:					
	Must be treated by a physician with expertise in the management of PAH, with this authority application to be completed by the physician with expertise in PAH;					
	AND					
	Treatment criteria:					
	Patient must ~~have~~ *be undergoing continuing treatment* ~~previously received stable doses~~ of *existing* PBS-subsidised macitentan and tadalafil as part of combination therapy (dual or triple therapy*, excluding selexipag*) *where macitentan and tadalafil and their doses in the combination remains unchanged from the previous authority application.*					

	Prescribing Instructions: This treatment is not PBS-subsidised for the use as initial therapy
	Prescribing Instructions: *For the purposes of PBS subsidy~~, an endothelin receptor antagonist is one of: (a) ambrisentan, (b) bosentan, (c) macitentan; a phosphodiesterase-5 inhibitor is one of: (d) sildenafil, (e) tadalafil;~~ a prostanoid is one of: (~~f~~a) epoprostenol, (~~g~~b) iloprost* *Authority applications for each agent in combination therapy should be made at the same time to reduce administrative handling. However, dosing of each agent need not occur simultaneously to be considered as 'combination triple therapy'.*
	Administrative Advice: *If this authority application is to continue combination therapy, but with a change in prostanoid, the 'Initial 3 – change' treatment phase restriction of the new drug outlines the continuing eligibility criteria of that new drug.*
	Administrative Advice: Special pricing arrangements apply
	Administrative Advice: *No increase in the maximum quantity or number of units may be authorised.*
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday)*
	Caution: *This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 3 months following cessation of therapy.*
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (~~Written~~ *Telephone/online PBS Authorities system*)
	Authority type: ☒ Complex Authority Required (CAR)
	Indication: Pulmonary arterial hypertension (PAH)
	Treatment Phase: Continuing treatment ~~–~~*of* combination therapy (triple therapy with selexipag)
	Clinical criteria:
	The treatment must ~~form~~ *be part* of triple combination therapy consisting of*: (i)* macitentan, *(ii)* tadalafil ~~and~~ *(iii) selexipag*
	Treatment criteria:
	Must be treated by a physician with expertise in the management of PAH, with this authority application to be completed by the physician with expertise in PAH;
	AND
	Treatment criteria:
	Patient must ~~have~~ *be undergoing continuing treatment* ~~previously received stable doses~~ of *existing* PBS-subsidised macitentan and tadalafil as part of combination therapy (*triple therapy with selexipag*) *where macitentan and tadalafil and their doses in the combination remains unchanged from the previous authority application.*

	Prescribing Instructions: This treatment is not PBS-subsidised for the use as initial therapy
	Prescribing Instructions: *The authority application for selexipag must be approved prior to the authority application for this agent*
	Administrative Advice: Special pricing arrangements apply
	Administrative Advice: *No increase in the maximum quantity or number of units may be authorised.*
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*
	Administrative Advice: *Authority applications for each agent in combination therapy should be made at the same time to reduce administrative handling. However, dosing of each agent need not occur simultaneously to be considered as 'combination triple therapy'.*
	Caution: *This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 3 months following cessation of therapy.*

3.2 The submission stated the European Society of Cardiology and the European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of PAH, which are utilised by Australian clinicians and medical associations (e.g. the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ)), recommend the regular monitoring and risk assessment of PAH patients every 3-6 months. The ESC agreed with the evaluation and advised that, for continuing treatment with MAC+TAD FDC, treatment criteria be added so that a patient must have been taking macitentan 10 mg and tadalafil 40 mg (as dual therapy, or as part of triple therapy) for 6 months (equivalent to the length of the prescription authority) prior to continuing treatment with the FDC. The ESC noted that this aligns with the ESC/ERS guidelines and PHSANZ's recommended 3 to 6 month follow up.

3.3 The submission requested an effective approved ex-manufacturer price (AEMP) for MAC+TAD FDC of $[redacted] based on the sum of the current effective AEMP for macitentan 10 mg tablet 30 pack for combination therapy of $[redacted], and the 30-day-equivelent AEMP for the tadalafil 20 mg tablet 56 pack ($509.51; calculated as $475.54 ÷ 28 days x 30 days). The submission noted that macitentan 10 mg is expected to undergo a 5% statutory price reduction from 1 April 2025.

3.4 The submission requested that a special pricing arrangement (SPA) apply for MAC+TAD FDC. The proposed published AEMP of MAC+TAD FDC is $3,242.16.

3.5 Macitentan is currently listed with an SPA, where the published AEMP is $2,732.65. The effective AEMP is $[redacted] based on a weighted price of monotherapy at an effective AEMP of $[redacted], and dual therapy at an effective AEMP of $[redacted] (weightings are [redacted]% monotherapy and [redacted]% dual therapy).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 PAH is a rare and debilitating chronic disease of the pulmonary vasculature, characterised by vascular proliferation, and remodelling of the small pulmonary arteries. This results in a progressive increase in pulmonary vascular resistance that, if not treated, ultimately leads to right heart failure and premature death. There is no cure for PAH other than lung transplantation. Symptoms of PAH include shortness of breath, dizziness, chest pain and fatigue (Post-market review of PAH Medicines minutes, PBAC Meeting November 2018).

4.2 The disease severity of PAH is classified according to a system of WHO functional classes (Post-market review of PAH Medicines minutes, PBAC Meeting November 2018). These four classes are:

- WHO FC I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.
- WHO FC II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
- WHO FC III – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.
- WHO FC IV – Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated the use of separate doses of one macitentan 10 mg tablet with two 20 mg tadalafil tablets as dual therapy, or with a prostanoid as triple therapy, as the main comparator. The evaluation also noted that one tablet of macitentan 10 mg in combination with two 20 mg tadalafil tablets is also PBS-listed for use as triple therapy, in combination with selexipag.

5.2 The submission stated that, since the requested restriction requires a patient to be stable on macitentan 10 mg and tadalafil 40 mg (2x20 mg) as separate doses prior to moving to the MAC+TAD FDC, it is the only therapy that can be replaced by the FDC in clinical practice and other combination therapies are not appropriate comparators. The submission also noted that the current clinical advice states that if patients fail to

achieve or maintain WHO FC II and are tolerating treatment, then medication from a different drug class should be added to the current treatment until the disease is under control. The submission stated that changes to existing medication regimens are often due to intolerable side effects which are less likely in patients who are receiving stable dosing of medications over extended periods of time.

5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.4 Subsection 101(4AC) of the *National Health Act 1953* requires the PBAC to advise the Minister when the committee is satisfied that therapy involving a combination item, compared with alternative therapies, provides one of the following for some patients:

- a significant improvement in patient compliance with the therapy
- a significant improvement in efficacy or reduction in toxicity.

5.5 For the requested population, the evaluation noted the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice by MAC+TAD FDC. Macitentan is an ERA and tadalafil is a PDE-5i.

- ERAs: bosentan and ambrisentan
- PDE-5i: sildenafil

5.6 Soluble guanylyl cyclase (sGC) stimulator, riociguat, is also PBS-listed for the treatment of PAH but cannot be used in combination therapy so is not considered an alternative therapy.

5.7 Table 3 lists the various combinations of drugs used in dual and triple therapy for PAH on the PBS. All combinations have a PBS indication that the patient must currently have WHO FC III or IV PAH. The ESC considered the ERA+PDE-5i combinations were relevant alternative therapies, except for combinations with bosentan (further discussion at paragraphs 6.15 - 6.16).

Table 3: PBS-listed combination therapies for PAH

Drug class combinations	PBS-listed drugs combinations
Dual therapy	
ERA AND PDE-5i	ambrisentan AND sildenafil ambrisentan AND tadalafil bosentan AND sildenafil bosentan AND tadalafil macitentan AND sildenafil macitentan AND tadalafil
ERA AND prostanoid	ambrisentan AND epoprostenol ambrisentan AND iloprost bosentan AND epoprostenol bosentan AND iloprost macitentan AND epoprostenol macitentan AND iloprost
ERA AND selexipag	ambrisentan AND selexipag bosentan AND selexipag macitentan AND selexipag
PDE-5i AND prostanoid	sildenafil AND epoprostenol sildenafil AND iloprost tadalafil AND epoprostenol tadalafil AND iloprost
PDE-5i AND selexipag	sildenafil AND selexipag tadalafil AND selexipag
Triple therapy	
ERA AND PDE-5i AND prostanoid	ambrisentan AND sildenafil AND epoprostenol ambrisentan AND sildenafil AND iloprost ambrisentan AND tadalafil AND epoprostenol ambrisentan AND tadalafil AND iloprost bosentan AND sildenafil AND epoprostenol bosentan AND sildenafil AND iloprost bosentan AND tadalafil AND epoprostenol bosentan AND tadalafil AND iloprost macitentan AND sildenafil AND epoprostenol macitentan AND sildenafil AND iloprost macitentan AND tadalafil AND epoprostenol macitentan AND tadalafil AND iloprost
ERA AND PDE-5i AND selexipag	ambrisentan AND sildenafil AND selexipag ambrisentan AND tadalafil AND selexipag bosentan AND sildenafil AND selexipag bosentan AND tadalafil AND selexipag macitentan AND sildenafil AND selexipag macitentan AND tadalafil AND selexipag

Compiled during the evaluation. Abbreviations: ERA = endothelin receptor antagonist; PDE-5i = phosphodiesterase-5 inhibitor

5.8 The pre-Sub-Committee Response (PSCR) cited the PBAC's recommendation of subcutaneous (SC) vedolizumab, for use as maintenance treatment in moderate to severe ulcerative colitis (MSUC) and severe Crohn's disease (CD), as a relevant precedent to refer to regarding alternative therapies. The PSCR noted the use of vedolizumab SC was for patients who have responded to the intravenous (IV) form of vedolizumab and thus is used in the maintenance treatment of these conditions. At its November 2020 meeting, the PBAC recommended the listing of vedolizumab (VDZ) SC for the treatment of MSUC and severe CD on a cost minimisation basis to VDZ IV. The

PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of VDZ SC would be acceptable if it were cost-minimised against VDZ IV. The ESC noted that VDZ IV had previously been recommended for listing against alternative therapies. That is, for the treatment of MSUC on a cost-minimisation basis with infliximab, and for severe CD on a cost-minimisation basis with infliximab and adalimumab, at the March 2015 PBAC meeting (paragraph 7.2, 7.06 vedolizumab Public Summary Document (PSD) and paragraph 7.2, 5.25 vedolizumab PSD, March 2015 PBAC meeting).

5.9 The ESC recalled that the PBAC has previously considered FDC products for type 2 diabetes mellitus (T2DM), as well as severe asthma and chronic obstructive pulmonary disease (COPD), where the sponsors were claiming non-inferior effectiveness and safety, and where the PBAC recommended that the cost of the proposed FDC be no greater than the cost of the lowest cost combination (comparator) (paragraph 7.6, dapagliflozin (DAPA) with sitagliptin (SITA) PSD, March 2024 PBAC Meeting; paragraph 7.2, beclomethasone (BEC) with formoterol (FOR) PSD, March 2022 PBAC Meeting). The pre-PBAC response argued that the DAPA/SITA precedent was not relevant to the request for MAC+TAD FDC, as in T2DM, physicians are more likely to move patients between individual drugs within a drug class, compared to PAH where clinical guidance recommends maintaining a patient on their initial therapy and adding another class of medicine instead. The pre-PBAC response also argued that BEC/FOR for COPD was not relevant to the request for MAC+TAD FDC, as the place in therapy for BEC/FOR is as an escalation treatment for patients who are not stable on a long-acting beta2-agonist (LABA) and requires the addition of an inhaled corticosteroid (ICS), whereas the MAC+TAD FDC is for continuing use in patients who are already stable on the individual components as combination therapy.

5.10 The PBAC recalled its March 2023 consideration of fosnetupitant/palonosetron (Akynzeo® IV), where it was considered reasonable that the financial comparator of the combination IV product should be the individual components in IV form and not the clinical oral comparators. This was considered acceptable as the recommended restriction prevented patients that could use oral anti-emetic medicines from accessing Akynzeo IV, and because other IV comparators would require additional dosages or oral maintenance doses until the next IV administration (paragraph 7.5, fosnetupitant (as chloride hydrochloride)/palonosetron PSD, March 2023 PBAC Meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from one organisation via the Consumer Comments facility on the PBS website. The Lung Foundation Australia discussed the health, financial and social cost for people living with PAH in Australia. The organisation was supportive of the proposed listing and stated that MAC+TAD FDC can potentially reduce pill burden and costs for these patients. The Lung Foundation Australia considered these reduced patient costs to be especially important for people with multiple co-morbidities.

Clinical evidence

6.3 The submission presented one clinical study, AC-077-103, assessing the bioequivalence and pharmacokinetics of the MAC+TAD FDC compared to use of macitentan and tadalafil dual therapy as individual tables. This was supplemented with the TGA Clinical Evaluation Report. A summary of the clinical evidence provided is listed in Table 4. The submission did not provide any references to the publications related to these studies; these details were added during the evaluation.

Table 4: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
AC-077-103	FINAL CLINICAL STUDY REPORT Single-center, open-label, single-dose, two-period, randomized, crossover, Phase 1 study to demonstrate bioequivalence between a fixed dose combination product formulation of macitentan/tadalafil (10 mg / 40 mg) and the free combination of 10 mg macitentan (Opsumit®) and 40 mg tadalafil (Adcirca®) in healthy male and female subjects	2018
	Grill S, Bruderer S, Sidharta PN, Antonova M, Globig S, Carlson J, Schultz A, Csonka D. Bioequivalence of macitentan and tadalafil given as fixed-dose combination or single-component tablets in healthy subjects.	Br J Clin Pharmacol. 2020 Dec;86(12):2424-2434.
Studies considered as part of the TGA Clinical Evaluation Report		
AC-077-101	Single-centre, open-label, single-dose, 2-period, randomised, crossover, Phase 1 study to demonstrate bioequivalence between 2 FDC product formulations of macitentan/tadalafil (10/40 mg) and the free combination of 10 mg macitentan and 40 mg tadalafil in healthy male and female participants.	2015
	Grill S, Bruderer S, Sidharta PN, Antonova M, Globig S, Carlson J, Schultz A, Csonka D. Bioequivalence of macitentan and tadalafil given as fixed-dose combination or single-component tablets in healthy subjects.	Br J Clin Pharmacol. 2020 Dec;86(12):2424-2434.
67896062PAH1006	Single-centre, open-label, single-dose, 2-period, randomised, crossover Phase 1 study to demonstrate bioequivalence of tadalafil administered as an FDC formulation of macitentan/tadalafil (10/40 mg) and as the free combination of 10 mg macitentan and 40 mg tadalafil, and to assess the effect of food on the PK of the FDC formulation of macitentan/tadalafil (10/40 mg) in healthy adult participants.	2020
	Csonka D, Fishman V, Natarajan J, Stieltjes H, Armas D, Dishy V, Perez Ruixo JJ. Bioequivalence and food effect of a fixed-dose combination of macitentan and tadalafil: Adaptive design in the COVID-19 pandemic.	Pharmacol Res Perspect. 2021 Oct;9(5):e00846. doi: 10.1002/prp2.846.
	Ford JL, Sabet A, Natarajan J, Stieltjes H, Chao DL, Goyal N, Csonka D. Bioequivalence, and the food effect of macitentan/tadalafil 10/20 fixed-dose combination tablets versus the use of single-component tablets in healthy subjects.	Pharmacol Res Perspect. 2024 Jun;12(3):e1202. doi: 10.1002/prp2.1202.

Compiled during the evaluation. Source: Section 9, pp 18-20 of the submission; TGA CER pp109-119

6.4 The submission stated that the AC-077-103 study proved that the FDC and the individual components were bioequivalent. With the addition of the other clinical studies, AC-077-101 and 67896062PAH1006, the TGA Delegate considered there was sufficient evidence that the MAC+TAD FDC was bioequivalent to treatment with macitentan and tadalafil as individual tablets.

6.5 The submission stated that during AC-077-103 no deaths, serious adverse events (AEs) or significant AEs were reported. The study showed similar AE profiles between the MAC+TAD FDC and macitentan and tadalafil as individual tablets, with no new safety concerns noted for the FDC. The TGA Delegate considered the safety profiles were appropriate for approval in a substitution indication.

Clinical claim

6.6 The submission claimed that MAC+TAD FDC 10 mg/40 mg was non-inferior in terms of efficacy and safety compared to the use of one 10 mg macitentan tablet and two 20 mg tadalafil tablets as combination therapy. The ESC considered that this claim was

reasonable based on the TGA's advice that the FDC is bioequivalent to treatment with the individual medicines.

6.7 The submission claimed that the reduced pill burden of 1 tablet compared to 3 that MAC+TAD FDC presents could improve adherance resulting in improved health outcomes for PAH patients. The submission presented studies and literature reviews which supported the claim that adherence to treatment for patients with PAH resulted in improved clinical outcomes[5]. The submisson also presented evidence that FDCs are generally associated with increased adherence to treatment as compared to loose doses of medicines[6]. The PSCR and pre-PBAC response reiterated that patients living with PAH experience a high pill burden due to multimorbidity and increasing age which results in an increased risk of non-compliance of their PAH combination therapy. The PSCR also stated that the introduction of the MAC+TAD FDC would have no barriers in clinical use and would provide improvement in convenience and likely adherence for patients stabilised on separate tablets of MAC 10 mg and two TAD 20 mg as combination therapy. No information was provided in the submission, PSCR, or pre-PBAC response to support MAC+TAD FDC increasing compliance and health outcomes for PAH directly.

6.8 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable based on the TGA's advice that the FDC is bioequivalent to treatment with the individual medicines.

Economic analysis

6.9 The submission presented a cost-minimisation approach versus combination therapy of one macitentan 10 mg tablet with two 20 mg tadalafil tablets.

6.10 The equi-effective doses were estimated as MAC+TAD FDC 10 mg/40 mg daily and macitentan 10 mg tablet with two 20 mg (40 mg) tadalafil tablets daily. This was reasonable and based upon the TGA's advice on bioequivalence.

6.11 The submission requested an effective AEMP for MAC+TAD FDC of $[redacted] based on the sum of the current effective AEMP for macitentan 10 mg tablet 30 pack for

[5] Farber et al. Real-world association between nonadherence to pulmonary arterial hypertension medications and clinical outcomes in the US. Chest 2023 Vol. 164 Issue 4 Pages A5945-A594.
Frantz et al. Medication adherence, hospitalization, and healthcare resource utilization and costs in patients with pulmonary arterial hypertension treated with endothelin receptor antagonists or phosphodiesterase type-5 inhibitors. Pulm Circ 2020 Vol. 10 Issue 1.
Qadus et al. Adherence and Discontinuation of Disease-Specific Therapies for Pulmonary Arterial Hypertension: A Systematic Review and Meta-Analysis. Am J Cardiovasc Drugs 2023 Vol. 23 Issue 1 Pages 19-33.

[6] Lauffenburger et al. Effect of Combination Therapy on Adherence Among US Patients Initiating Therapy for Hypertension: a Cohort Study. J Gen Intern Med 2017 Vol. 32 Issue 6 Pages 619-625
Paoli et al. Advantages of Fixed Dose Combination (FDC) Products over Loose Dose Combination (LDC) Products: A Systematic Literature Review (SLR). ISPOR US, Boston, MA, May 7-10, 2023.
Thom et al. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. JAMA 2013 Vol. 310 Issue 9 Pages 918-29.

combination therapy of $[redacted] and the 30-day-equivalent AEMP for the tadalafil 20 mg tablet 56 pack ($509.51; calculated as $475.54 ÷ 28 days x 30 days).

6.12 As noted in the comparator section, there are several alternative therapies for MAC+TAD (see Table 3). Table 5 lists the cost per day of treatment (based on effective AEMP) for MAC+TAD FDC compared to ERA+PDE-5i combinations which may be considered as alternative dual therapies.

Table 5: Submission cost-minimisation approach compared to alternative therapies cost per day

Therapy	Effective AEMPs of components	Pack size; dosage	Calculation	Price per day of treatment
Submission CMA				
MAC+TAD FDC 10 mg/40 mg	$[redacted]	30; 1 tablet/day	AEMP/30 days = $[redacted]/30	$[redacted]
macitentan 10 mg and 2 x tadalafil 20 mg	MAC = $[redacted] TAD = $475.54	MAC = 30; 1 tablet/day TAD = 56; 2 tablet/day	(MAC AEMP/30) + (TAD AEMP/56 * 2) = ($[redacted]/30) + ($475.54/56 * 2) = $[redacted] + $16.98	$[redacted]
Alternative therapies (dual therapy)				
bosentan 2 x 125 mg and sildenafil 3 x 20 mg	BOS = $169.30 SIL = $131.30	BOS = 60; 2 tablets/day SIL = 90; 3 tablets/day	(BOS AEMP/60 *2) + (SIL AEMP/90 * 3) = ($169.30/60*2) + ($131.30/90 * 3) = $5.64 + $4.38	$10.02
bosentan 2 x 125 mg and tadalafil 2 x 20 mg	BOS = $169.30 TAD = $475.54	BOS = 60; 2 tablets/day TAD = 56; 2 tablet/day	$5.64 + $16.98	$22.62
ambrisentan 5 mg and sildenafil 3 x 20 mg	AMB = $1,652.15 SIL = $131.30	AMB = 30; 1 tablet/day SIL = 90; 3 tablets/day	(AMB AEMP/30) + $4.38 = ($1,652.15/30) + $4.38 = $55.07 + $4.38	$59.45
ambrisentan 5 mg and tadalafil 2 x 20 mg	AMB = $1,652.15 TAD = $475.54	AMB = 30; 1 tablet/day TAD = 56; 2 tablet/day	$55.07 + $16.98	$72.05
macitentan 10 mg and sildenafill 3 x 20 mg	MAC = $[redacted] SIL = $131.30	MAC = 30; 1 tablet/day SIL = 90; 3 tablets/day	$[redacted] + $4.38	$[redacted]

Source: Submission CMA sourced from pp20-21 of the submission. Alternative therapies compiled during the evaluation.
Abbreviations: AMB = ambrisentan; BOS = bosentan; FDC = fixed dose combination; MAC = macitentan; SL = sildenafil; TAD = tadalafil.

6.13 No claim was made in the submission that MAC+TAD FDC has superior efficacy or safety over the existing alternative therapies. Under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

6.14 The PSCR and pre-PBAC response maintained that separate tablets of one macitentan 10 mg and two tadalafil 20 mg in combination therapy is the only relevant alternative therapy (i.e. comparator) for the MAC+TAD FDC, as it is the only combination therapy that could be replaced in clinical practice based on the MAC+TAD FDC TGA-approved indication, 2022 ESC/ERS Guidelines and PHSANZ recommendations. The PSCR and pre-PBAC response stated that, whilst it is highly unlikely and not appropriate or

allowed per the TGA indication and PBS restriction for patients on other ERA+PDE-5i combinations to switch directly to the MAC+TAD FDC, if this did occur, the MAC+TAD FDC would likely deliver superior efficacy and/or safety over lower cost combinations.

6.15 The ESC noted previous PBAC advice from the November 2019 PBAC meeting where 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 equi-effectiveness of bosentan/PDE-5i combinations compared to other ERA/PDE-5i combinations, as well as current clinical guidelines and clinician concerns over increased hepatotoxicity with bosentan, 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. The PBAC also considered that the price of tadalafil should be comparable to that of sildenafil (para 5.24, Post-market review of PAH Medicines minutes, PBAC Meeting November 2019). The ESC noted bosentan's usage in clinical practice is limited because of the known safety concerns.

6.16 The ESC considered that, should the clinical claim of overall non-inferior effectiveness and safety be accepted, then the PBAC will need to advise on the cost-minimisation approach and if the cost per patient for treatment with the MAC+TAD FDC should be no more than the cost per patient of any other available ERA+PDE-5i combination. The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapies. The ESC expressed concern around the safety of bosentan which was consistent with PBAC's November 2019 advice regarding price benchmarking for ERA/PDE-5i combination and advised that the next lowest priced combination to bosentan and sildenafil may be a more appropriate choice of lower cost combination.

Drug cost/patient/year

6.17 The estimated drug cost per patient per year of MAC+TAD FDC based on effective price is $ (Public) and $ (Private), based on 12 scripts per year and an effective dispensed price for maximum quantity (DPMQ) of $ (Public) and $ (Private).

Table 6: Drug cost per patient for proposed and comparator drugs (using effective AEMP/DPMQ)

	MAC+TAD FDC 10 mg/40 mg HSD Public	MAC+TAD FDC 10 mg/40 mg HSD Private	MAC 10 mg and TAD 2x20 mg HSD Public	MAC 10 mg and TAD 2x20 mg HSD Private
Dose	FDC 10 mg/40 mg		MAC 10 mg and TAD 2x 20 mg	
Duration	Daily, continuous		Daily, continuous	
Cost/patient/month	$	$[a]	MAC: $ (30 days) TAD: $475.54 (28 days)	MAC: $[a] (30 days) TAD: $503.23 (28 days)
Cost/patient/year	$	$	= ($ + $6,182.02)[b] = $[c]	= ($ + $6,541.99) [b] = $

Compiled during the evaluation, Source: Table 5 p.21 of Submission Main Body and the Utilisation and cost model workbook. Abbreviations: AEMP = approved ex-manufacturer price; DPMQ = dispense price for maximum quantity; FDC = fixed dose combination; MAC = macitentan; TAD = tadalafil.

Note that under the PBS pricing for Section 100 HSD Public hospital scripts, AEMP = DPMQ.

a. Effective DPMQ for Private HSD scripts = Effective AEMP + PBS ready-prepared dispensing fee plus a mark-up of $40 for drugs with an ex-manufacturer price of greater than $1000. Therefore, the effective DPMQ for MAC+TAD FDC at the time of evaluation = $ + $8.67 + $40 = $
b. Calculated as 12 scripts/year for macitentan and 13 scripts per year of tadalafil
c. Using the DPMQ for the 60 pack of tadalafil of $509.51 and the assumption of 12 scripts/year (as the 60 pack provides 30 days of treatment) the cost/patient/year for public scripts is the same as the MAC+TAD FDC public script cost of $.

Estimated PBS usage & financial implications

6.18 This submission was not considered by DUSC. The submission presented a market share approach to estimating the PBS usage and financial implications. The submission expected no market growth in the number of patients treated, as the requested restriction did not propose any changes compared to the current restrictions for MAC and TAD combination therapy in PAH and required prior stabilisation on MAC and TAD as individual medicines. The submission assumed that MAC+TAD FDC would only replace existing macitentan 10 mg tablets and tadalafil 40 mg (20 mg x 2) use as separate tablets.

6.19 The submission used PBS 10% sample data provided by Prospection Pty Ltd to calculate the number of patients in 2021, 2022 and 2023 who had been supplied both macitentan 10 mg and tadalafil 40 mg (2x 20 mg) prescriptions concurrently for at least 3 months. The submission assumed that 3 months of concurrent treatment was equivalent to establishing stability on the dual therapy. These patient numbers were converted to scripts per year and then extrapolated for 2025 to 2030. The number of affected scripts for macitentan 10 mg and tadalafil 20 mg were assumed each to be equivalent to the number of scripts for the FDC (one script for macitentan 10 mg, one script for tadalafil 20 mg). The tadalafil scripts estimated were then adjusted for the smaller pack size requiring more scripts per 12 months.

Table 7: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Estimated current usage (scripts)	Estimation of patients per year on both MAC and TAD for at least 3 months for 2021, 2022, 2023 using 10% PBS data Conversion to scripts per year if on MAC+TAD FDC Extrapolation of 3 year script trends to present 2025-2030 script numbers	Appropriate. The evaluation verified Prospection's analysis which was used to estimate the number of patients using concomitant MAC and TAD and noted it is representative of the 100% PBS population.
Estimated existing scripts of MAC in combination with TAD as separate pills > 3 months	Extrapolation of 3 year script trends (2021 – 2023) from 10% PBS data. Patients were only assumed to be on combination therapy if there was at least 3 months of overlapping scripts for MAC and TAD. Year 1: [redacted][1] Year 2: [redacted][1] Year 3: [redacted][1] Year 4: [redacted][1] Year 5: [redacted][1] Year 6: [redacted][1]	
Uptake rate	70% in Year 1 increasing to 80% for Years 2 - 6. Based on pill burden reduction of 3 to 1.	The ESC considered that this assumption was reasonable.
Annual growth rate	Estimated from extrapolation of the 3 year script trends from 10% PBS data 2025: MAC 7.66%, TAD 23.04% 2026: MAC 6.44%, TAD 6.44% 2027: MAC 5.55%, TAD 5.55% 2028: MAC 4.88%, TAD 4.88% 2029: MAC 4.36%, TAD 4.36%	Appropriate. The sponsor has assumed that the market will stabilise with declining growth in the outer years rather than a linear forecast.
Public/Private split	78.41% Public 21.59% Private Using 2023 Services Australia PBS/RPBS dispensed script data	Appropriate. The sponsor used 100% PBS data for the relevant PBS item numbers for the year 2023. .
Scripts/patient/year	12 scripts of MAC+TAD FDC; assumed 30 pack is equivalent to 1 months' supply MAC: 12 TAD: 12.86	The submission did not provide an explicit number of scripts per patient per year for the TAD scripts. The submission adjusted the affected TAD scripts by multiplying the affected MAC scripts by 30/28 (30 days of MAC treatment/28 days TAD treatment) = 1.071. The evaluation multiplied 12 scripts by 1.071 to obtain the 12.86 TAD scripts per person per year, assuming the 56-tablet pack size.
Calculation of offsets: Price of MAC applied	Effective AEMP of $[redacted] applied, based on the weighted price across the dual and monotherapy settings	The evaluation noted the indication-specific AEMP for the dual-therapy setting ($[redacted]) should have been used as this was applied in the submission's CMA

Compiled during the evaluation. Source: Financial estimates pp21-24 of the submission. Sheet 2e Scripts – market of Utilisation and cost model workbook. AEMP = approved ex-manufacturer price; DPMQ = dispense price for maximum quantity; FDC = fixed dose combination; MAC = macitentan; TAD = tadalafil.

The redacted values correspond to the following ranges:

[1] 10,000 to < 20,000

6.20 Table 8 shows the estimated financial impact of listing MAC+TAD FDC over the next 6 years.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of MAC+TAD FDC						
Number of scripts dispensed[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of MAC+TAD FDC						
Cost to PBS/RPBS less copay	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][4]
Estimated implications for replaced macitentan and tadalafil (AEMP $[redacted] applied in the submission, based on the weighted price across the dual and monotherapy settings in submission)						
Macitentan 10 mg scripts replaced[b]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Tadalafil 20 mg scripts replaced[c]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Authorities processed by Services Australia	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Cost to PBS/RPBS less copay	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net financial implications						
Net cost to PBS/RPBS	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Re-estimated during evaluation using indication-specific price of macitentan in the dual-therapy setting (AEMP $[redacted])						
Estimated implications for replaced macitentan and tadalafil						
Cost to PBS/RPBS less copay	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]

Source: Table 7, pp24-25, Table 13, p. 25 of the submission, Sheet 6. Net changes – SA of Utilisation and cost model workbook. AEMP = approved ex-manufacturer price; DPMQ = dispense price for maximum quantity; FDC = fixed dose combination; MAC = macitentan; TAD = tadalafil.

[a] Assuming 12 scripts per person per year as estimated by the submission.

[b] Assuming 12 scripts per person per year.

[c] Assuming 12.86 scripts per person per year.

The redacted values correspond to the following ranges:

[1] 10,000 to < 20,000

[2] $20 million to < $30 million

[3] $30 million to < $40 million

[4] $40 million to < $50 million

[5] net cost saving

[6] $0 to < $10 million

6.21 The financial implications to the PBS/RPBS of listing MAC+TAD FDC was estimated to be a net cost saving in Year 6, with a net cost saving in the first 6 years of listing. However, the majority of this cost saving was due to the way offsets for the reduced use of macitentan 10 mg tablets were applied. The submission based these offsets on the weighted price across the mono- and dual-therapy settings. When the relevant indication-specific price was applied (using the dual-therapy macitentan price of $[redacted], as applied in the CMA), the total financial impact to the PBS/RPBS was a net extra cost of approximately $0 to < $10 million over six years. The PSCR maintained the weighted average price of monotherapy and dual therapy approach presented in the submission was appropriate. The ESC noted the reduction in script volumes as a result of listing a FDC product would lead to a reduction in co-payments which is likely the cause of the net cost to Government.

6.22 The submission's estimated cost savings also result from the difference in the total amount of scripts required for the 56 pack of tadalafil compared to the proposed

30 pack FDC. The savings may be further overestimated as patients that are currently prescribed the 60 pack of tadalafil would not require extra scripts.

6.23 The submission considered that MAC+TAD FDC would only replace scripts for patients who are currently stable on macitentan 10 mg and tadalafil 40 mg (2 x 20 mg). This was supported by the argument that the restriction is only for continuing use of macitentan and tadalafil dual therapy, or triple therapy containing macitentan and tadalafil, where the patient is stable on the 10 mg macitentan/40 mg tadalafil dose.

6.24 The submission did not consider whether listing MAC+TAD FDC as a continuation option would lead to prescribers initiating patients on the macitentan 10 mg and tadalafil 40 mg (2x 20 mg) treatment regimen over other combination therapies. The ESC considered that some clinicians may prefer to initiate patients with PAH on macitentan and tadalafil in preference to other possible combinations if they felt that eventual change to the MAC+TAD FDC would improve adherence and patient acceptability of therapy. The estimates may therefore underestimate the impact of listing the MAC+TAD FDC on the PBS budget, as this could lead to the replacement of lower cost medicines.

6.25 If the PBAC were to recommend a cost-minimisation approach to an alternative ERA+PDE-5i combination therapy with a lower effective AEMP, MAC+TAD FDC listing may result in cost savings to the PBS/RPBS.

6.26 The evaluation noted that the PBS listing of MAC+TAD FDC may reduce administrative burden for clinicians and the Government. Patients on continuing therapy currently require separate authority prescriptions for both MAC and TAD whereas MAC+TAD FDC would require only one authority prescription. Additionally, MAC+TAD FDC would reduce the number of authority scripts that Services Australia would be required to process.

Quality Use of Medicines

6.27 The submission noted that there may be quality use of medicines concerns regarding transitioning patients stable on separate doses of macitentan and tadalafil tablets to the MAC+TAD FDC. The submission noted that patients would need support with the transition as they are familiar with their current dosage regimen. The submission stated that the applicant has ensured the following to reduce quality use of medicines concerns:

- the MAC+TAD FDC packaging and tablets are clearly distinguishable from the individual dose tablets, with a different tablet shape to the macitentan 10 mg tablet and different shape and colouring to the tadalafil 20 mg tablet.
- a quality use of medicines program is being developed with plans to implement one month prior to PBS listing, with an education program for prescribers, pharmacists and nurses, and print, digital and in person resources for health care professionals and patients.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Highly Specialised Drug Program) Authority Required (Telephone/Online) listing of macitentan 10 mg with tadalafil 40 mg (Opsynvi®, herein referred to as MAC+TAD) fixed dose combination (FDC) for the continuing treatment of pulmonary arterial hypertension (PAH) in patients who are on stable doses of macitentan and tadalafil as combination therapy. The PBAC's recommendation was based on, among other matters, its assessment that the cost-effectiveness of MAC+TAD FDC would be acceptable if it were cost-minimised against the dual therapy components prices of one macitentan 10 mg tablets with two x 20 mg tadalafil tablets.

7.2 The PBAC noted that the intention of the proposed listing is that only patients that are stable on macitentan 10 mg and tadalafil 40 mg (as two 20 mg tablets) doses are eligible for MAC+TAD FDC. The PBAC considered that it was appropriate for treatment criteria for MAC+TAD FDC initiation to be added so that a patient must have been taking macitentan 10 mg and tadalafil 40 mg (as dual therapy, or as part of triple therapy) for at least 6 months (equivalent to the length of the prescription authority) prior to continuing onto the FDC. The PBAC noted that this aligns with the European Society of Cardiology and the European Respiratory Society (ECS/ERS) guidelines and the recommended 3 to 6 month follow up from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ).

7.3 The PBAC noted the endothelin receptor agonists (ERA) and phosphodiesterase-5 inhibitors (PDE-5i) combinations presented in Table 3 but considered concomitant macitentan with tadalafil to be the appropriate comparator given the most likely patients to use the MAC+TAD FDC are patients already stabilised on both of the specific components. This was supported by the TGA-approved indication, the proposed restriction, and clinical guidelines.

7.4 The PBAC noted the TGA's advice that MAC+TAD FDC is bioequivalent to treatment with the individual medicines (one macitentan 10 mg tablet and two 20 mg tadalafil tablets). The PBAC therefore accepted the submission's clinical claim of non-inferior comparative effectiveness and safety.

7.5 The PBAC advised that MAC+TAD FDC would be cost effective if cost-minimised to the cost of the equivalent dose of macitentan and tadalafil as individual components. The PBAC advised that the price of macitentan specific for use in combination therapy (as proposed by the submission) was appropriate. The PBAC noted that the equi-effective doses used in the cost-minimisation analysis (CMA) were consistent with the TGA's advice on bioequivalence. The PBAC advised that the equi-effective doses are MAC+TAD FDC 10 mg/40 mg daily and one macitentan 10 mg tablet with two 20 mg (40 mg) tadalafil tablets daily.

7.6 The PBAC considered the reduction in script volumes as a result of listing a FDC product would lead to a reduction in co-payments and therefore a net cost to Government. However, the PBAC considered this cost was unlikely to be significant as it would be driven by patient numbers and would be outweighed by the improvement in patient adherence to therapy, and therefore clinical outcomes; the reduction in pill burden for those patients; and reduction in administrative burden for prescribers.

7.7 The PBAC noted the submission estimated a 70-80% uptake rate based on pill burden reduction. The PBAC agreed with the ESC that the uptake rate used to estimate the number of eligible patients treated was reasonable.

7.8 The PBAC recommended that MAC+TAD FDC should not be treated as interchangeable with any other drugs.

7.9 The PBAC advised that MAC+TAD FDC is not suitable for prescribing by nurse practitioners.

7.10 The PBAC recommended that the Early Supply Rule should not apply to MAC+TAD FDC, noting that the Early Supply Rule does not apply to macitentan or tadalafil.

7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because MAC+TAD FDC is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over concomitant macitentan and tadalafil, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
MACITENTAN + TADALAFIL					
macitentan 10 mg + tadalafil 40 mg tablet, ~~oral~~ *30*	NEW	1	30	5	Opsynvi
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (Telephone/online PBS Authorities system)				
	Authority type: ☒ Complex Authority Required (CAR)				

	Indication: Pulmonary arterial hypertension (PAH)
	Treatment Phase: Continuing treatment of combination therapy (dual or triple therapy, excluding selexipag)
	Clinical criteria:
	The treatment must be dual combination therapy as a fixed dose combination consisting of: (i) macitentan (ii) tadalafil; or
	The treatment must be part of triple combination therapy as a fixed dose combination consisting of: (i) macitentan, (ii) tadalafil (iii) one prostanoid.
	Treatment criteria:
	Must be treated by a physician with expertise in the management of PAH, with this authority application to be completed by the physician with expertise in PAH;
	AND
	Treatment criteria:
	Patient must be undergoing continuing treatment of existing PBS-subsidised macitentan and tadalafil as part of combination therapy (dual or triple therapy, excluding selexipag) where macitentan and tadalafil and their doses in the combination remains unchanged from the previous authority application.
	Prescribing Instructions: This treatment is not PBS-subsidised for the use as initial therapy
	Prescribing Instructions: For the purposes of PBS subsidy, a prostanoid is one of: (a) epoprostenol, (b) iloprost Authority applications for each agent in combination therapy should be made at the same time to reduce administrative handling. However, dosing of each agent need not occur simultaneously to be considered as 'combination' therapy.
	Administrative Advice: If this authority application is to continue combination therapy, but with a change in prostanoid, the 'Initial 3 – change' treatment phase restriction of the new drug outlines the continuing eligibility criteria of that new drug.
	Administrative Advice: Special pricing arrangements apply
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday)
	Caution: This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 3 months following cessation of therapy.
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (Telephone/online PBS Authorities system)
	Authority type: ☒ Complex Authority Required (CAR)

	Indication: Pulmonary arterial hypertension (PAH)
	Treatment Phase: Continuing treatment *of* combination therapy (triple therapy with selexipag)
	Clinical criteria:
	The treatment must be part of triple combination therapy consisting of: (i) macitentan, (ii) tadalafil (iii) selexipag
	Treatment criteria:
	Must be treated by a physician with expertise in the management of PAH, with this authority application to be completed by the physician with expertise in PAH;
	AND
	Treatment criteria:
	Patient must be undergoing continuing treatment of existing PBS-subsidised macitentan and tadalafil as part of combination therapy (triple therapy with selexipag) where macitentan and tadalafil and their doses in the combination remains unchanged from the previous authority application.
	Prescribing Instructions: This treatment is not PBS-subsidised for the use as initial therapy
	Prescribing Instructions: The authority application for selexipag must be approved prior to the authority application for this agent
	Administrative Advice: Special pricing arrangements apply
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
	Administrative Advice: Authority applications for each agent in combination therapy should be made at the same time to reduce administrative handling. However, dosing of each agent need not occur simultaneously to be considered as 'combination therapy'.
	Caution: This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 3 months following cessation of therapy.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available

through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.

11 Corrigendum

The following changes were made:

Change made	Date of revision
Paragraph 7.1: Authority required (Written) amended to Authority required (Telephone/Online) to reflect the recommended authority level elsewhere in the document.	19 March 2025