

**7.09 MAVACAMTEN,  
Capsule 2.5 mg,  
Capsule 5 mg,  
Capsule 10 mg,  
Capsule 15 mg,  
Camzyos<sup>®</sup>,  
Bristol Myers Squibb Australia Pty Ltd**

**1 Purpose**

- 1.1 The early re-entry resubmission requested a General Schedule Authority Required listing for mavacamten for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (HCM).
- 1.2 This resubmission was based on the PBAC decision to not recommend mavacamten for this indication from July 2023. The PBAC had also previously decided not to recommend mavacamten for this indication in November 2022. This current resubmission addressed all but one of the issues raised by PBAC in July 2023; see Table 1 below.

**Table 1: Summary of key matters to be addressed**

<b>Matter of concern (July 2023 PSD)</b>	<b>Response</b>	<b>Addressed?</b>
Revision to the restriction as outlined in paragraphs 7.4 to 7.6:		
i) the proposed restriction should reflect the peak LVOT gradient from the EXPLORER-HCM trial ( $\geq 50$ mm Hg at rest, after Valsalva manoeuvre or exercise)	i) proposed a PBS restriction that only includes patients with a peak LVOT gradient $\geq 50$ mm Hg (at rest or with provocation (Valsalva manoeuvre or post exercise)).	Y
ii) continuing treatment with mavacamten would require demonstration of ongoing clinical response	ii) proposed the following wording for the PBAC's consideration: 'Consideration should be given to discontinue treatment in patients who have shown no response (e.g., no improvement in symptoms, quality of life, exercise capacity, or LVOT gradient) after 4-6 months on the maximum tolerated dose.'	Y
iii) appropriate to position mavacamten after a patient remained symptomatic after previously receiving trials of <u>both</u> a BB and a CCB (unless intolerant/contraindicated to one or both) rather than after a trial of either a BB or CCB.	iii) proposed a PBS restriction that requires patients to have had prior treatment with both a BB and CCB unless intolerant or contraindicated.	Y
iv) the proposed restriction should include a definition of familial HCM (i.e. first degree relatives).	iv) accepted the PBAC Secretariat's proposed wording that familial HCM be defined as 'at least one first degree relative with a diagnosis of hypertrophic cardiomyopathy'	Y

Matter of concern (July 2023 PSD)	Response	Addressed?
<p>Revision to the economic model as outlined in paragraphs 7.11 and 7.13:</p> <p>i) a respecified base case should also include <u>more conservative assumptions for mortality, hospitalisation and SRT rates</u>. A respecified base case was estimated during PBAC consideration using parameters the PBAC advised should be applied to the economic model (details in Table 16 of the PSD):</p> <ul style="list-style-type: none"> <li>• 20-year time horizon</li> <li>• TP truncation at 30 weeks both arms</li> <li>• Removal of mortality benefits</li> <li>• Reduced by half for CV rates: NYHA II (i.e. 0.38 →0.19) and NYHA III/IV patients (i.e. 1.00 →0.50)</li> <li>• Patients (%) escalating from mavacamten to SRT using VALOR-HCM (all NYHA classes: 3.6%).</li> </ul> <p>ii) a price reduction that results in an ICER of not more than \$45,000 per QALY gained;</p>	<p>- included more conservative assumptions for mortality and SRT rates, aligned Table 16 of the July 2023 PSD: mortality benefit is removed; patients (%) escalating from mavacamten to SRT using VALOR-HCM (all NYHA classes: 3.6%).</p> <p>- provided new evidence (Charron et al (unpublished)) which shows that hospitalisations increase with NYHA class; proposed that the assumptions specific to hospitalisation rates remain as detailed in the July 2023 resubmission, i.e. CV hospitalisation rates: NYHA II, 0.38 and NYHA III/IV, 1.00</p> <p>ii) offered a █████% price reduction from AEMP \$█ to \$█ for mavacamten (28 pack) with a resultant ICER of \$█<sup>1</sup>/QALY gained</p>	<p>Y</p> <p>N</p> <p>Y</p>
<p>A revised RSA inclusive of a 100% rebate to Government for expenditure over the subsidisation cap using the revised financial estimates with a reduced drug price as outlined in paragraphs 7.12 and 7.13.</p>	<p>Financial estimates include:</p> <ul style="list-style-type: none"> <li>- reduced mavacamten ex-manufacturer price (\$█ per 28 capsule pack)</li> <li>- updated fees and markups due to indexation from 1 July 2023</li> <li>- updated MBS cost for items 55126 and 55134 from 1 July 2023</li> <li>- change to first year of listing (now 2024)</li> <li>- an RSA inclusive of a █████% rebate above the subsidisation cap</li> </ul>	<p>Y</p>

Source: Mavacamten PSD July 2023 PBAC; November 2023 mavacamten early re-entry resubmission

BB = beta blocker; CCB = calcium channel blocker; HCM = hypertrophic cardiomyopathy; ICER = incremental cost-effectiveness ratio; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; PSD = Public Summary Document; RSA = risk sharing arrangement; SRT = septal reduction therapy; TP = transition probability.

The redacted values correspond to the following ranges:

<sup>1</sup> \$35,000 to < \$45,000

## 2 Background

### Registration status

2.1 Mavacamten was TGA registered on 15 September 2022 for the treatment of adults with symptomatic NYHA class II-III obstructive HCM. The product information was revised on 17 July 2023, with the addition in a boxed warning of the risk of heart failure due to systolic dysfunction. The special warnings and precautions for use notes that patients with a serious intercurrent illness such as serious infections or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia) or those

undergoing major cardiac surgery may be at greater risk of systolic dysfunction and progress to heart failure.

### Previous consideration

2.2 In July 2023, the PBAC did not recommend the listing of mavacamten for the treatment of adults with symptomatic obstructive HCM. The PBAC considered that mavacamten ± beta blocker/calcium channel blocker (BB/CCB) provided a moderate and important clinical benefit over standard of care (BB/CCB) in terms of symptomatic improvement, however considered a number of issues remained unresolved in the resubmission. These issues included the proposed place in therapy, the uncertain impact of mavacamten on long-term clinical endpoints, such as hospitalisations and mortality, and a number of optimistic assumptions related to clinical benefit in the economic model that were not supported by clinical trial evidence, that led to an uncertain and underestimated incremental cost-effectiveness ratio (ICER) (paragraph 7.1, mavacamten Public Summary Document [PSD], July 2023 PBAC meeting)

2.3 In July 2023, the PBAC considered the following changes may address these outstanding issues without requiring further re-evaluation:

- revision to the restriction as outlined in paragraphs 7.4 to 7.6;
- revision to the economic model as outlined in paragraph 7.11;
- a price reduction that results in an ICER of not more than \$45,000 per QALY gained;
- a revised RSA inclusive of a 100% rebate to Government for expenditure over the subsidisation cap using the revised financial estimates with a reduced drug price (paragraph 7.13, mavacamten PSD, July 2023 PBAC meeting).

See Table 1 above for further detail.

2.4 The PICO from the previous submission is presented below.

**Table 2: Key components of the clinical issue addressed by the resubmission**

Component	Description
Population	Adult patients with symptomatic obstructive hypertrophic cardiomyopathy
Intervention	Mavacamten ± BB/CCB
Comparator	BBs or CCBs (SOC) as per the pivotal clinical trial EXPLORER-HCM.
Outcomes	Primary: an improvement of ≥1.5 mL/kg/min mixed venous oxygen tension (pVO2) and a reduction of ≥1 class in NYHA Functional Class (Composite 1) OR; an improvement of ≥3.0 mL/kg/min in pVO2 with no worsening in NYHA Functional Class (Composite 2).
Clinical claim	Mavacamten ± BB/CCB is superior in terms of efficacy to monotherapy BBs or CCBs. Mavacamten ± BB/CCB has an inferior but manageable safety profile to monotherapy BBs or CCBs.

Source: Table 1, mavacamten PSD, July 2023.

BB = beta-blockers; CCB = calcium channel blockers; kg = kilogram; mg = milligram; NYHA = New York Heart Association; pVO2 = peak oxygen consumption; SOC = standard of care.

### 3 Requested listing

- 3.1 In July 2023, the PBAC considered the appropriate authority level was a written authority listing for initial therapy and a telephone/online PBS authority for continuing therapy, including a requirement for clinical monitoring by cardiologists or consultant physicians with experience in the management of HCM.
- 3.2 In the July 2023 commentary, the PBAC Secretariat had proposed PBAC consider an additional restriction option that was inclusive of all treatment phases with suggested authority type (telephone/electronic). In this resubmission, two listing options were proposed for the PBAC's consideration: (1) an 'all treatment phase' restriction; and (2) separate initial, continuing and grandfather restrictions. The resubmission's proposed initial and continuing listings are presented below in Table 3 and Table 4 below. Additions proposed by the Secretariat are in italics and deletions are in strikethrough.
- 3.3 The pre-PBAC response suggested that:
- An LVEF threshold of <50%, not 55%, would be appropriate for the continuing and discontinuation phases, given the PI instruction that, 'If at any clinical visit LVEF is <50%, treatment should be interrupted. Restart treatment after 4 weeks at one lower dose level (e.g., 5 to 2.5 mg; 10 to 5 mg; 15 to 10 mg) if LVEF ≥50%. Patients on 2.5 mg who temporarily interrupted treatment on two consecutive occasions because their LVEF remains <50% should discontinue treatment'.
  - The continuing response assessment should be at 4–6 months on the optimal dose of mavacamten, rather than 4–6 months after treatment initiation per the Secretariat suggestions. The pre-PBAC response noted that per the PI, the earliest timepoint a patient can titrate to the 10 mg and 15 mg dose is at 12 and 24 weeks respectively, and considered that assessment at 4–6 months after initiation may not allow sufficient time for a patient to demonstrate response at these doses.
  - The initial phase repeats should be increased from 2 to 5, to allow for 6 months treatment in total and adequate time to demonstrate response. The pre-PBAC response noted that mavacamten requires titration and individualised dosing based on echocardiogram, and as such the timeframe in which patients transition to maintenance therapy will vary.
- 3.4 The resubmission did not specify a published DPMQ but special pricing arrangements are requested. The revised effective DPMQ is \$|. The pre-PBAC response confirmed the proposed published DPMQ was as previously requested from July 2023, that is \$2,312.92.

Table 3: Initial Restriction

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MAVACAMTEN					
mavacamten 2.5 mg capsule, 28	NEW	1	28	2	Camzyos®
mavacamten 5 mg capsule, 28	NEW	1	28	2	Camzyos®
<b>Restriction Summary [new 1] / Treatment of Concept: [new 2]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction Type:</b> <input checked="" type="checkbox"/> immediate/real-time assessment by Services Australia via the online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail; requires at least one concept ID to be marked as 'FULL' for full assessment by Services Australia)					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative Advice:</b> Special Pricing Arrangements apply.					
<b>Administrative Advice:</b> Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.					
<b>Caution:</b> The patient's condition should be assessed prior to receiving treatment and closely monitored throughout the treatment period.					
<b>Condition:</b> Symptomatic obstructive hypertrophic cardiomyopathy					
<b>Indication:</b> Symptomatic obstructive hypertrophic cardiomyopathy					
<b>Treatment Phase:</b> Initial treatment					
<b>Clinical criteria:</b>					
Patient must have confirmed left ventricular hypertrophy due to hypertrophic cardiomyopathy with maximal left ventricular wall thickness at least one of either: (i) no less than 15 mm, OR (ii) no less than 13 mm if patient has familial hypertrophic cardiomyopathy (at least one first degree relative with a diagnosis of hypertrophic cardiomyopathy)					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have confirmed peak left ventricular outflow tract (LVOT) gradient of no less than 50mm Hg, which is measured either: (i) at rest, or (ii) after provocation with at least one of (i) Valsalva manoeuvre, (ii) exercise.					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have a <del>current documented</del> left ventricular ejection fraction (LVEF) of no less than 55%,					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have had prior treatment with both a (i) beta-blocker and (ii) non-dihydropyridine calcium channel blocker, unless at least one of the following is present: (i) a contraindication to beta-blocker <i>and/or</i> non-dihydropyridine calcium channel blocker therapy as listed in the TGA approved Product Information, (ii) an intolerance to beta-blocker <i>and/or</i> non-dihydropyridine calcium channel blocker therapy.					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must be undergoing treatment with at least one of (i) a beta-blocker (ii) non-dihydropyridine calcium channel blocker, unless at least one of the following is present:					

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(i)	a contraindication to beta-blocker <i>and/or</i> non-dihydropyridine calcium channel blocker therapy as listed in the TGA approved Product Information,
(ii)	an intolerance to beta-blocker <i>and/or</i> non-dihydropyridine calcium channel blocker therapy.
<b>AND</b>	
<b>Clinical criteria:</b>	
Patient must be symptomatic with NYHA classes II or III	
<b>Treatment criteria:</b>	
Must be treated by a cardiologist; or	
Must be treated by a consultant physician with experience in the management of hypertrophic cardiomyopathy	
<b>Population criteria:</b>	
Patient must be at least 18 years of age.	
<b>Administrative Advice:</b>	
The authority application must be made via the online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail and must include details (date, unique identifying number/code or provider number) of the echocardiogram or cardiac MRI report confirming:	
1. the diagnosis of hypertrophic cardiomyopathy (confirmed left ventricular hypertrophy due to HCM with maximal left ventricular wall thickness) of either:	
(i)	no less than 15mm or
(ii)	no less than 13mm if patient has familial HCM (at least one first degree relative with a diagnosis of hypertrophic cardiomyopathy); and
2. peak left ventricular outflow tract (LVOT) gradient of no less than 50mm Hg, prior to commencing treatment with this drug which is measured either:	
(i)	at rest, OR
(ii)	after provocation with at least one of (a) Valsalva manoeuvre, (b) exercise; and
3. left ventricular ejection fraction (LVEF) of no less than 55%.	
All <i>results and</i> reports must be documented in the patient's medical records.	
If the application is submitted through HPOS form upload or mail, it must include:	
(i)	A completed authority prescription form; and
(ii)	A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

**Table 4: Continuing Treatment**

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
MAVACAMTEN					
mavacamten 2.5 mg capsule, 28	NEW	1	28	5	Camzyos®
mavacamten 5 mg capsule, 28	NEW	1	28	5	Camzyos®
mavacamten 10 mg capsule, 28	NEW	1	28	5	Camzyos®
mavacamten 15 mg capsule, 28	NEW	1	28	5	Camzyos®
Restriction Summary [new 3] / Treatment of Concept: [new 4]					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)					

<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Administrative Advice:</b> Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
<b>Condition:</b> Symptomatic obstructive hypertrophic cardiomyopathy
<b>Indication:</b> Symptomatic obstructive hypertrophic cardiomyopathy
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition,
<b>AND</b>
<b>Clinical criteria:</b>
Patient must be undergoing treatment with at least one of (i) a beta-blocker (ii) non-dihydropyridine calcium channel blocker, unless at least one of the following is present:
(i) a contraindication to beta-blocker / non-dihydropyridine calcium channel blocker therapy as listed in the TGA approved Product Information,
(ii) an intolerance to beta-blocker / non-dihydropyridine calcium channel blocker therapy.
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have a <del>current documented</del> left ventricular ejection fraction (LVEF) of no less than 55%,
<b>AND</b>
<b>Clinical criteria:</b>
<del>Consideration should be given to discontinue treatment in patients who have shown no response (e.g., no improvement in symptoms, quality of life, exercise capacity, or LVOT gradient) after 4–6 months on the maximum tolerated dose.</del> Patient must have demonstrated a response after 4–6 months of mavacamten treatment defined as an improvement in at least one of the following: (i) symptoms, (ii) quality of life, (iii) exercise capacity, (iv) LVOT gradient.
<b>AND</b>
<b>Treatment criteria:</b>
Must be treated by a cardiologist; or
Must be treated by a consultant physician with experience in the management of hypertrophic cardiomyopathy
<b>AND</b>
<b>Population criteria:</b>
Patient must be at least 18 years of age.
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

*For more detail on PBAC's view, see section 5 PBAC outcome*

## 4 Consideration of the evidence

### **Sponsor hearing**

4.1 There was no hearing for this item.

### **Consumer comments**

4.2 In addition to comments previously received, the PBAC noted and welcomed the input from an additional individual via the Consumer Comments facility on the PBS website. The comment described the expected benefits of treatment with mavacamten in

terms of symptom relief, quality of life and reduced need for major surgery. The PBAC noted that the clinical evidence supported a moderate improvement in symptom relief.

### **Economic analysis**

- 4.3 The resubmission provided a revised economic model in line with the PBAC advice from July 2023, as detailed in Table 1. The only disputed change related to hospitalisations rates for HCM, which have been modelled to increase by NYHA class. The proposed CV hospitalisation rates were based on an Advisory Board survey of 9 cardiologists and remained unchanged from the November 2022 and July 2023 submissions. The PBAC had previously considered a more conservative approach would be appropriate and suggested halving the CV hospitalisations rates: NYHA II (i.e. 0.38 →0.19) and NYHA III/IV patients (i.e. 1.00 →0.50). This resubmission argued for no change to the previously modelled CV hospitalisation rates based on 2 pieces of supportive evidence: Charron et al (unpublished), a draft manuscript being prepared for submission by the end of 2023 to the journal *Circulation: Cardiovascular Quality and Outcomes* (published by the American Heart Association); and Wang et al 2023, an abstract submitted to the American Heart Association 2023 conference, previously presented in the July 2023 pre-PBAC response.
- 4.4 Charron et al (unpublished) reports on a retrospective observational study of patients with obstructive HCM in current clinical practice in France using claims data from the Système National Des Données de Santé (SNDS) database. The patients were included into the study from 1 January 2012 to 31 December 2018. Overall, there were 6,823 patients with obstructive HCM during the study period. This study reports hospitalisation events for patients with obstructive HCM. Patients in NYHA Class II were hospitalised on average 0.51 times per year for HCM-related reasons. Those in NYHA Class III were hospitalised 0.71 times per year on average and those in NYHA Class IV 1.14 times per year. Values were higher for those who were hospitalised for any cardiovascular-related reason, 0.74 times per year for NYHA Class II patients, 1.21 for NYHA Class III and 2.28 for NYHA Class IV.
- 4.5 Wang et al (2023), which was also presented in the July 2023 pre-PBAC response, was a factor considered by PBAC in suggesting halving CV hospitalisation rates rather than removing them altogether (paragraph 6.49, mavacamten PSD, July 2023 PBAC meeting). Wang et al (2023) used Optum’s de-identified Market Clarity database (administrative claims linked with electronic health records [EHR]) from 1 January 2017 to 31 March 2022. This study reported data on 754 patients and hospitalisation rates by NYHA class. The report indicated that on average, NYHA Class II patients are hospitalised once per year, NYHA III 1.6 times per year and NYHA IV 2.1 times per year.
- 4.6 The resubmission argued that despite potential differences across countries, data collection and reporting methods, these 2 studies indicate that hospitalisations rates increase by NYHA class and numerically these rates may be higher than the hospitalisation rates in the economic model considered at the July 2023 PBAC

meeting. The resubmission therefore argued that halving the current hospitalisation rates is not appropriate and maintained that the rates used in the economic model, which are average values derived from a survey of Australian clinicians expert in the treatment of obstructive HCM, are reasonable and represent the most appropriate inputs.

- 4.7 The revised economic model included:
- A 20-year time horizon
  - Transition probability truncation at 30 weeks both arms
  - Removal of mortality benefits
  - CV hospitalisation rates: NYHA II (0.38); NYHA III/IV patients (1.00)
  - Patients (%) escalating from mavacamten to SRT using VALOR-HCM (all NYHA classes: 3.6%).
  - % price reduction (AEMP \$) reduced from AEMP \$ in July 2023).
- 4.8 The revised ICER was \$35,000 to < \$45,000/QALY gained.
- 4.9 The pre-PBAC response highlighted an additional Spanish observational, retrospective study CV027-051 on hospitalisations by NYHA class (unpublished), which it considered showed consistent results with Charron et al (unpublished) and Wang et al (2023).

### ***Estimated PBS usage & financial implications***

- 4.10 This resubmission provided updated financial implications. The estimates included the following changes:
- Reduced mavacamten ex-manufacturer price (\$) per 28 capsule pack)
  - Updated fees and markups due to indexation from 1 July 2023
  - Updated MBS cost for items 55126 and 55134 from 1 July 2023
  - Change to first year of listing (now 2024)
  - Presentation of an RSA inclusive of a % rebate above the subsidisation cap
- 4.11 These revised estimates align with the updated assumptions provided in the July 2023 pre-subcommittee response, as advised by the PBAC July 2023 (paragraph 7.12, mavacamten PSD). A summary of key assumptions is presented in Table 5.

**Table 5: Summary of key sources of information and assumptions used in the financial estimates**

Base case model inputs		November 2022	July 2023	November 2023	Comments
Eligible obstructive HCM population	Prevalence of HCM	1 in 350 Australians	1 in 350 Australians	1 in 350 Australians	Unchanged
	Diagnosis rate of HCM	10.95%, increasing by 20% per year	N/A	N/A	Removed in line with DUSC advice
	Proportion of patients with obstructive HCM	37.70%	60.94%	60.94%	Increased in response to DUSC comment regarding uncertainty of LVOT gradient used to determine access to mavacamten
	Proportion of obstructive HCM patients who are NYHA Class II or III	49.54%	49.54%	49.54%	Unchanged
	Proportion of obstructive HCM patients with LVEF $\geq 55$	88.92%	88.92%	88.92%	Unchanged
	Proportion of patients not well controlled on BB/CCB	N/A	44.29%	44.29%	Informed by Advisory Board input and available data from the academic literature
Compliance		97.56%	97.56%	97.56%	Unchanged
Persistence		Year 1: 66.10% Year 2+: 93.94%	N/A	N/A	Removed in line with DUSC advice (persistent population is no longer used in the modelling of financial impact)
Uptake (among eligible patients)		71.11%	71.11%	71.11%	Unchanged
PBS/RPBS split	PBS	97.37%	97.44%	97.46%	Updated to use latest available PBS Item Statistics data (December 2021 – December 2022) for sacubitril + valsartan (Entresto®)
	RPBS	2.63%	2.56%	2.54%	
Discontinuation rate		N/A	N/A	5.00% at 30 weeks; 8.53% annually thereafter	Presented in July 2023 PSCR and confirmed in pre-PBAC response, added in line with commentary request
Transthoracic echocardiogram (TTE)		\$240.05	\$240.05	\$248.70	Fee for MBS items 55126 and 55134 A total of 6 TTE in Year 1 and 4.5 each year thereafter (12 weekly).

Source: Table 6 resubmission, p18

BB = beta-blocker; CCB = calcium channel blocker; DUSC = Drug Utilisation Sub Committee; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; PBS = Pharmaceutical Benefits Scheme; PSCR = pre-subcommittee response; RPBS = Repatriation Pharmaceutical Benefits Scheme

4.12 The estimated use and financial impacts of listing mavacamten are provided in Table 6.

**Table 6: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed <sup>a</sup>	2	2	3	3	3	4
<b>Estimated financial implications</b>						
Net cost to PBS/RPBS	5	5	5	6	6	6
Net cost to MBS	7	7	7	7	7	7
Net cost to SA	7	7	7	7	7	7
Net cost to Australian Government (PBS/RPBS/MBS/SA)	8	5	5	5	6	6
<b>Previous submission July 2023 (PSCR)</b>						
Net cost to PBS/RPBS	9	10	10	8	8	8
<b>Previous submission November 2022 (pre-PBAC response)</b>						
Net cost to PBS/RPBS	11	12	12	12	12	12

<sup>a</sup>worksheet 3a of Mavacamten-obstructive HCM-Utilisation and Cost Model-Early-Re-entry-Resubmission.xlsx.

Source: Tables, 8, 11, 14 and 15 of the resubmission; July 2023 and November 2022 mavacamten minutes

PBS = Pharmaceutical Benefits Scheme; PSCR = pre-subcommittee response; RPBS = Repatriation Pharmaceutical Benefits Scheme; SA = Services Australia

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 50,000 to < 60,000

<sup>3</sup> 40,000 to < 50,000

<sup>4</sup> 30,000 to < 40,000

<sup>5</sup> \$40 million to < \$50 million

<sup>6</sup> \$30 million to < \$40 million

<sup>7</sup> \$0 to < \$10 million

<sup>8</sup> \$50 million to < \$60 million

<sup>9</sup> \$70 million to < \$80 million

<sup>10</sup> \$60 million to < \$70 million

<sup>11</sup> \$90 million to < \$100 million

<sup>12</sup> \$100 million to < \$200 million

4.13 The estimated cost to the PBS/RPBS of listing mavacamten for obstructive HCM ranged from \$40 million to < \$50 million to \$30 million to < \$40 million per year, with a cumulative total of \$200 million to < \$300 million over the first 6 years of listing. Including MBS and Service Australia costs, the net cost to Government over 6 years is estimated to be \$200 million to < \$300 million.

### **Financial Management – Risk Sharing Arrangements**

4.14 In July 2023, the PBAC considered that a resubmission should include a revised RSA inclusive of a 100% rebate to Government for expenditure over the subsidisation cap

using the revised financial estimates with a reduced drug price (paragraph 7.13, mavacamten PSD, July 2023 PBAC meeting).

- 4.15 The resubmission presented a proposed subsidisation cap below, based on net cost to PBS/RPBS, above which the sponsor will pay a  $\frac{1}{2}$ % rebate for additional utilisation.

**Table 7: Proposed risk sharing arrangement subsidisation cap**

	2024	2025	2026	2027	2028
Net cost to PBS/RPBS (\$)	1	1	1	1	1

Source: Table 16, p 26 of resubmission. Calculations from Worksheet 3c. Impact - proposed (eff), 'Mavacamten obstructive HCM Utilisation and Cost Model-Early-Re-entry-Resubmission'.

*For more detail on PBAC's view, see section 5 PBAC outcome*

## 5 PBAC Outcome

- 5.1 The PBAC recommended the listing of mavacamten for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (HCM). The PBAC is satisfied that mavacamten provides, for some patients, a significant improvement in efficacy over standard of care, in terms of symptomatic improvement, and it would be cost effective at the reduced price proposed in the resubmission.
- 5.2 The PBAC considered that the resubmission had addressed the substantive outstanding issues identified at the July 2023 meeting via a revised restriction, revised economic modelling, a price reduction, revised financial estimates, and an RSA proposal with a  $\frac{1}{2}$ % rebate above the subsidisation cap.
- 5.3 The PBAC recalled that it had considered, based on the key EXPLORER-HCM trial, that mavacamten provided only a moderate improvement in symptomatic outcomes, that the trial did not demonstrate improvement in quality-of-life measures (para 7.7, July 2023 PSD), and that the long-term comparative effectiveness and safety was unknown (para 7.6, November 2022 PSD). However, in the context of the unmet need for additional treatments for HCM, and the consumer comments that described the very negative impact of the disease on daily life, the PBAC considered that even this moderate improvement would be of significant benefit for some patients. The PBAC noted that mavacamten was the first drug which had undergone a randomised, double blind placebo control for use in obstructive HCM.
- 5.4 The PBAC noted that the TGA Product Information had been updated on 17 July 2023, with the addition in a boxed warning of the risk of heart failure due to systolic dysfunction. The PBAC noted that the pre-PBAC response proposed continuing and grandfather restriction phases require that a patient have a current LVEF of no less than 50%. The PBAC advised this was appropriate as it was consistent with the PI advice that treatment interruption may be necessary to ensure LVEF remains  $\geq 50\%$ . LVEF at initiation needs to remain at  $\geq 55\%$ .

- 5.5 In terms of the clinical place in therapy and the PBS restriction, the PBAC noted that the resubmission had appropriately: restricted use to only patients with a peak LVOT gradient  $\geq 50$  mm Hg (at rest or with provocation (Valsalva manoeuvre or post exercise); positioned mavacamten after separate trials of both a BB and CCB unless intolerant or contraindicated; and included a definition of familial HCM (i.e. first degree relatives). The PBAC advised that separate initial, continuing and grandfathering phase listings were appropriate given the different authority levels, the evidentiary requirements for initiation and the response requirement for continuation. In the continuing phase restriction, the resubmission appropriately included a clinical criterion regarding demonstrating treatment response. The PBAC advised that as PBS clinical criteria are legal requirements, the proposed criterion wording be amended from a suggestion to prescribers ('Consideration should be given...') into a requirement ('Patient must have...'), as per the Secretariat proposed wording.
- 5.6 The PBAC reaffirmed its previous decision that the appropriate authority level was a written authority listing for initial therapy and a telephone/online PBS authority for continuing therapy. The written authority would require provision of reports, capturing wall thickness and LVOT gradient as well as other diagnostic information for patients with familial HCM. Current and prior history of BB and CBB use, including any contraindications or intolerance should also be captured.
- 5.7 Further to this, the PBAC noted the pre-PBAC response request for additional repeats in the initial phase to ensure patients had sufficient time to titrate and demonstrate a response. Given the critical importance of dose titration as per the TGA PI with frequent reassessment of LVEF by echocardiogram, as well as the requirement to demonstrate a response, the PBAC considered it most appropriate to split the restriction into several phases.
- Initial restriction: 2.5 mg and 5 mg only and 2 repeats (allowing a total of 12 weeks treatment)
  - 1st continuing restriction: all strengths available and 2 repeats (allowing a total of another 12 weeks of treatment to finish dose titration)
  - 2nd continuing restriction: all strengths available and 5 repeats (allowing 6 months on a stable, optimal dose to assess response)
  - Maintenance treatment: all strengths and 5 repeats, with demonstration of a response after at least 6 months on the optimal dose, defined as improvement in symptoms, quality of life, exercise capacity, or LVOT gradient.
- 5.8 The PBAC advised the grandfathering restriction should be a written authority and that it provide adequate options for dose titration and 6 months on stable, optimal dosing to be able to assess response before patients become eligible for maintenance treatment.

- 5.9 With respect to the economic model, the PBAC noted that the resubmission had included more conservative assumptions for mortality and SRT rates (per Table 16 of the July 2023 PSD), truncation at 30 weeks in both arms, and incorporated a lower price resulting in an ICER less than \$45,000 per QALY gained, as per previous PBAC advice. However, with new supporting evidence (Charron et al, unpublished), the resubmission had argued against changing the hospitalisation rates from the July 2023 resubmission. The PBAC noted there was limited reliable data to inform this parameter and remained of the view that the model's hospitalisation rates were likely overestimated; however, noting the new supporting evidence, the PBAC considered, its previous suggestion of reducing these rates by 50% was potentially too conservative. The PBAC considered that, with the tightened response criteria in the continuation restriction, the listing would still be cost-effective using the hospitalisation rates from July 2023 resubmission.
- 5.10 The PBAC recalled that it had previously considered the approach to the financial estimates was acceptable (para 7.12, PSD, July 2023 PBAC meeting), and noted that the current resubmission had appropriately incorporated the reduced price and proposed an RSA with a 1% rebate, in line with the PBAC's advice. The PBAC noted that although the financial impact was very high, the financial estimates had been substantially reduced from the original mavacamten submission.
- 5.11 The PBAC advised that mavacamten is not suitable for prescribing by nurse practitioners.
- 5.12 The PBAC recommended that the Early Supply Rule should not apply given the variable dosing.
- 5.13 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for mavacamten:
- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, because only a moderate improvement in symptoms was seen in the key trial;
  - b) The treatment is not expected to address a high and urgent unmet clinical need because although treatment options are limited, and symptoms impact on quality of life, patients with this condition are expected to have similar mortality as the general population;
  - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 5.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## **6 Recommended listing**

6.1 Add new item: Restriction wording to be finalised.

## **7 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.

## **8 Sponsor's Comment**

Bristol-Myers Squibb Australia welcomes this recommendation by the PBAC and looks forward to continuing to work with the Department of Health and Aged Care to provide access to mavacamten for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (HCM).