

**7.03 MAVACAMTEN,
Capsule 2.5 mg, Capsule 5 mg, Capsule 10 mg,
Capsule 15 mg,
Camzyos[®],
Bristol Myers Squibb Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a Section 85, General Schedule Authority Required listing for mavacamten for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (HCM).
- 1.2 Listing was requested based on a cost-effectiveness analysis versus standard of care (SOC) (beta-blocker (BB) or calcium channel blocker (CCB)). The key components of the request are summarised in Table 1.

Table 1: 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 (standard of care (SOC)) as per the pivotal clinical trial EXPLORER-HCM.
Outcomes	Primary: An improvement of ≥ 1.5 mL/kg/min mixed venous oxygen tension (pVO ₂) and a reduction of ≥ 1 class in New York Heart Association (NYHA) Functional Class (Composite 1) OR; An improvement of ≥ 3.0 mL/kg/min in pVO ₂ 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 <u>inferior but manageable</u> safety profile to monotherapy BBs or CCBs.

Source: Table 1, p12 of the submission.

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

Blue shading represents information previously considered by the PBAC.

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.

Previous PBAC consideration

- 2.2 Table 2 summarises the key matters of concern from the November 2022 submission.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Restriction		This was unchanged in the resubmission.

Public Summary Document – July 2023 PBAC Meeting

Component	Matter of concern	How the resubmission addresses it
	<p>The PBAC noted that the proposed PBS restriction for peak LVOT gradient (≥ 30 mmHg) was broader than the inclusion criteria in EXPLORER-HCM (≥ 50 mmHg) and considered the restriction should reflect the higher peak LVOT gradient (≥ 50 mmHg at rest, after Valsalva manoeuvre or exercise) from EXPLORER-HCM. (para.3.3 & 7.4. mavacamten, Public Summary Document, November 2022 PBAC meeting). The PBAC also stated that removal of the proposed restriction allowing use of mavacamten prior to BB treatment (where local guidelines allow it) was appropriate. (para. 7.4. mavacamten, Public Summary Document, November 2022 PBAC meeting).</p> <p>The PBAC considered a telephone/online PBS authority was required given the proposed assessments for monitoring will require echocardiograms and treatment by cardiologists or consultant physicians with experience in the management of hypertrophic cardiomyopathy (para. 7.3. mavacamten, Public Summary Document, November 2022 PBAC meeting).</p>	<p>The resubmission presented four main arguments (pp27-28) in support of the LVOT gradient criteria being ≥ 30 mmHg. Arguments were based on international guidelines (European Society of Cardiology; AHA/ACC); eligibility criteria for EXPLORER-HCM with analysis for baseline characteristics; the proportion of patients with LVOT between 30 and 50 mmHg being small (3.4% of patients) in an epidemiology study by Maron et al., (2006)); and proposal of an RSA. Addressed. Criterion was removed from the initiation restriction in the resubmission.</p> <p>Addressed. Administrative changes were made to the continuing restriction in the resubmission.</p>
Surrogate outcomes	<p>The PBAC noted that the EXPLORER-HCM reported on symptomatic/functional endpoints only. The effect mavacamten has on other patient relevant outcomes such as hospitalisation and mortality cannot be practically evaluated in trials in HCM patients because these events are rare. There is no evidence that deaths would be reduced with mavacamten and patients with HCM are expected to have normal life expectancy; mavacamten is therefore not expected to provide mortality benefits. (para 7.6. mavacamten, Public Summary Document, November 2022 PBAC meeting).</p>	<p>The resubmission conducted a targeted literature search citing seven references to support the primary composite surrogate outcome to predict death and hospitalisations:</p> <ul style="list-style-type: none"> • Fiuzal et al., (2020) • Karapolat et al., (2008) • SHaRe (Tompkins et al., 2018.) • Bennett et al., (2002) • Gallagher et al., (2019) • SHaRe registry (Lakdawala et al., 2022) • Wang et al., (2022)
Clinical claim	<p>The PBAC considered the claim of superior comparative effectiveness was reasonable, but the claim of non-inferior safety compared with SOC was not adequately supported by the data (para. 6.33, 6.34, and 7.7, mavacamten, Public Summary Document, November 2022 meeting).</p>	<p>Addressed. The clinical claim was revised in the resubmission to superior comparative effectiveness and inferior comparative safety versus SOC.</p>

Public Summary Document – July 2023 PBAC Meeting

Component	Matter of concern	How the resubmission addresses it
Base case economic model	<p>The PBAC noted several key issues with the economic model that had been raised by the evaluation and the ESC. The PBAC considered a respecified base case should include the following:</p> <ul style="list-style-type: none"> • a 10-year time horizon • truncation at 30 weeks in both arms • no mortality benefit • amended inputs for: <ul style="list-style-type: none"> - cardiovascular hospitalisation rates and costs - SRT costs - disopyramide benefits - discontinuation rates <p>(para. 7.8 & 7.9, mavacamten, Public Summary Document, November 2022 PBAC meeting).</p>	<p>The updated economic model was amended to include:</p> <ul style="list-style-type: none"> • a 20-year time horizon (instead of 10-year) • truncation at 38 weeks in SOC arm only (revised from 46 weeks) • amended inputs for: <ul style="list-style-type: none"> - cardiovascular hospitalisation costs - removal of disopyramide from model structure. - discontinuation due to SAEs at week 30 and annually. <p>The updated economic model did not amend parameters pertaining to:</p> <ul style="list-style-type: none"> • removal of mortality benefit • inputs for: <ul style="list-style-type: none"> - cardiovascular hospitalisation rates - SRT costs • discontinuation of mavacamten due to lack of efficacy.
Financial estimates and risk share	<p>Due to the high variability associated with the measure (LVOT) and possibility of mavacamten monotherapy to replace SOC treatment, the PBAC stated an RSA should be considered given that there is a high risk of use in patients with less severe disease (para. 7.10. mavacamten, Public Summary Document, November 2022 PBAC meeting).</p>	<p>The resubmission revised the financial estimates, incorporating the changes in the economic model and using the lower effective DPMQ. The resubmission proposed that any expenditure over and above the subsidisation cap be subject to a █████% rebate to Government. The proposed subsidisation cap covers a five-year period from 2023 to 2027 (totalling \$█████² over 5 years). The financial impact was forecast in the resubmission to be \$█████¹ million over 6 years.</p>

Source: para. 3.3, 7.4, 7.6, 7.8, 7.9, 7.10, mavacamten, Public Summary Document, November 2022 PBAC meeting, and the main body of the resubmission.

ACC = American College of Cardiology; AHS = American Heart Association; BB= beta-blockers; DPMQ = dispensed price per maximum quantity; ESC = Economic Sub Committee; HCM = hypertrophic cardiomyopathy; LVOT = left ventricular outflow tract; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RSA= Risk Share Agreement; SAE = serious adverse events; SOC = Standard of Care; SRT = Septal Reduction Therapy.

The redacted values correspond to the following ranges:

¹ \$400 million to < \$500 million

² \$300 million to < \$400 million

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

3 Requested listing

3.1 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	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®

Public Summary Document – July 2023 PBAC Meeting

Restriction Summary [new 1] / Treatment of Concept: [new 2]
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as ‘FULL’ for full assessment by Services Australia)
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient’s medical records.
Caution: <i>The patient's condition should be assessed prior to receiving treatment and closely monitored throughout the treatment period.</i>
Condition: Symptomatic obstructive hypertrophic cardiomyopathy
Indication: Symptomatic obstructive hypertrophic cardiomyopathy
Treatment Phase: Initial treatment
Clinical criteria: Patient must have confirmed left ventricular hypertrophy due to hypertrophic cardiomyopathy with maximal left ventricular wall thickness which is either <i>at least one of:</i> (i) greater than or equal to <i>no less than</i> 15 mm, or (ii) greater than or equal to <i>no less than</i> 13 mm if patient has familial hypertrophic cardiomyopathy (<i>at least one first degree relative with a diagnosis of hypertrophic cardiomyopathy</i>)
AND
Clinical criteria: Patient must have confirmed peak left ventricular outflow tract (LVOT) gradient of greater than or equal to <i>no less than</i> 30 50mm Hg which is measured either: (i) at rest, or (ii) after provocation with either <i>at least one of</i> (i) Valsalva manoeuvre, or (ii) exercise.
AND
Clinical criteria: Patient must have a documented left ventricular ejection fraction (LVEF) of greater than or equal to <i>no less than</i> 55%,
AND
Clinical criteria: Patient must be undergoing <i>have received</i> prior treatment with either <i>a</i> either a (i) a beta-blocker or (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 existing / expected intolerance to beta-blocker / non-dihydropyridine calcium channel blocker therapy.
AND
Clinical criteria: Patient must be symptomatic with NYHA classes II or III
Treatment criteria: Must be treated by a cardiologist; or Must be treated by a consultant physician with experience in the management of hypertrophic cardiomyopathy
Population criteria: Patient must be at least 18 years of age.

Public Summary Document – July 2023 PBAC Meeting

Administrative Advice:

The authority application must be made in writing and must include:

(1) a completed authority prescription form; and

(2) 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).

Administrative Advice:

Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au

Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos

Or mailed to:

Services Australia

Complex Drugs

Reply Paid 9826

HOBART TAS 7001

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]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.					
Condition: Symptomatic obstructive hypertrophic cardiomyopathy					
Indication: Symptomatic obstructive hypertrophic cardiomyopathy					
Treatment Phase: Continuing treatment					
Clinical criteria:					

Public Summary Document – July 2023 PBAC Meeting

Patient must have previously received PBS-subsidised treatment with this drug for this condition,
AND
Clinical criteria:
The treatment must be administered in combination with either a beta blocker and/or a non-dihydropyridine CCB unless intolerant or contra-indicated. Patient must be undergoing treatment with either a (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.
AND
Clinical criteria:
Patient must have a documented left ventricular ejection fraction (LVEF) of greater than or equal to no less than 55%,
Treatment criteria:
Must be treated by a cardiologist; or
Must be treated by a consultant physician with experience in the management of hypertrophic cardiomyopathy
Population criteria:
Patient must be aged at least 18 years of age or older .
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).

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 5] / Treatment of Concept: [new 6]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives					
Restriction Type: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as ‘FULL’ for full assessment by Services Australia)					
Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a ‘Grandfathered’ patient must qualify under the ‘Continuing treatment’ criteria.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.					
Administrative Advice: This Grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria.					

Public Summary Document – July 2023 PBAC Meeting

Condition: Symptomatic obstructive hypertrophic cardiomyopathy
Indication: Symptomatic obstructive hypertrophic cardiomyopathy
Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment – ‘grandfather’ arrangements
Clinical criteria:
Patient must be receiving non-PBS-subsidised treatment with this drug for this indication which commenced prior to [1 Month 20XX]
AND
Clinical criteria:
<i>Patient must have confirmed left ventricular hypertrophy due to hypertrophic cardiomyopathy with maximal left ventricular wall thickness prior to commencing non-PBS subsidised treatment which is at least one of:</i>
<ul style="list-style-type: none"> (i) no less than 15 mm, (ii) no less than 13 mm if patient has familial hypertrophic cardiomyopathy (at least one first degree relative with a diagnosis of hypertrophic cardiomyopathy)
AND
Clinical criteria:
<i>Patient must have confirmed peak left ventricular outflow tract (LVOT) gradient of no less than 50mm Hg prior commencing non-PBS subsidised treatment which is measured either:</i>
<ul style="list-style-type: none"> (i) at rest, (ii) after provocation with at least one of (i) Valsalva manoeuvre, (ii) exercise.
AND
Clinical criteria:
The treatment must be administered in combination with either a beta blocker and/or a non-dihydropyridine CCB unless intolerant or contra-indicated.
<i>Patient must be undergoing treatment with either a (i) a beta-blocker (ii) non-dihydropyridine calcium channel blocker, unless at least one of the following is present</i>
<ul style="list-style-type: none"> (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.
AND
Clinical criteria:
Patient must have a documented left ventricular ejection fraction (LVEF) of greater than or equal to no less than 55%,
AND
Clinical criteria:
<i>Patient must have been symptomatic with NYHA classes II or III prior to commencing non-PBS subsidised treatment</i>
Treatment criteria:
Must be treated by a cardiologist; or
Must be treated by a consultant physician with experience in the management of hypertrophic cardiomyopathy.
Population criteria:
Patient must be at least aged 18 years of age or older .
Administrative Advice:
<i>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</i>
<i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au</i>
<i>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</i>

Public Summary Document – July 2023 PBAC Meeting

Or mailed to:

Services Australia

Complex Drugs

Reply Paid 9826

HOBART TAS 7001

Another option:

One restriction for all treatment phases as per the secretariat suggestion:

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 1] / Treatment of Concept: [new 2]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)					
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: Special Pricing Arrangements apply.					
Administrative Advice: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.					
Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.					
Caution: The patient's condition should be assessed prior to receiving treatment and closely monitored throughout the treatment period.					
Indication: Symptomatic obstructive hypertrophic cardiomyopathy					
Clinical criteria: Patient must have confirmed left ventricular hypertrophy due to hypertrophic cardiomyopathy with maximal left ventricular wall thickness which is at least one of: (i) no less than 15 mm, (ii) no less than 13 mm if patient has familial hypertrophic cardiomyopathy (at least one first degree relative with a diagnosis of hypertrophic cardiomyopathy)					

Public Summary Document – July 2023 PBAC Meeting

AND
Clinical criteria:
Patient must have confirmed 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, (ii) after provocation with at least one of (a) Valsalva manoeuvre, (b) exercise.
AND
Clinical criteria:
Patient must have a documented left ventricular ejection fraction (LVEF) of no less than 55%,
AND
Clinical criteria:
Patient must be undergoing treatment with either a (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.
AND
Clinical criteria:
Patient must be symptomatic with NYHA classes II or III prior to commencing treatment with this drug
Prescribing instructions:
Titration in the dose is expected according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised. A medical practitioner must not request the maximum listed number of repeats if lesser repeats are sufficient for the patient's needs.
Treatment criteria:
Must be treated by a cardiologist; or
Must be treated by a consultant physician with experience in the management of hypertrophic cardiomyopathy
Population criteria:
Patient must be at least 18 years of age.
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).

- 3.2 The requested effective price (AEMP \$[REDACTED]) is [REDACTED]% lower than that proposed in the November 2022 submission (AEMP \$[REDACTED]). The resubmission proposed an effective DPMQ of \$[REDACTED] and a published DPMQ of \$2,312.92.
- 3.3 The proposed restriction outlined in the November 2022 submission included a clinical criterion restricting access to patients with symptomatic obstructive HCM with a peak left ventricular outflow tract (LVOT) gradient ≥ 30 mmHg (at rest, after Valsalva manoeuvre or exercise). This remained unchanged in the resubmission. At the November 2022 meeting, the PBAC stated that the restriction should include a criterion restricting access to patients with peak LVOT gradient ≥ 50 mm Hg (at rest,

after Valsalva manoeuvre or exercise). The ESC and PBAC previously agreed with the Pre-Sub-Committee Response (PSCR), which stated that peak LVOT gradient is a highly variable measure of disease severity. The PBAC agreed with the ESC that the restriction should reflect the higher peak LVOT gradient from the pivotal trial (EXPLORER-HCM). The PBAC stated that due to the high variability associated with the measure (LVOT), a risk sharing arrangement (RSA) should be considered given that there is a high risk of use in patients with less severe disease (para. 3.3, mavacamten, Public Summary Document, November 2022 PBAC meeting).

- 3.4 The resubmission presented four main arguments in support of retaining the LVOT gradient criterion at ≥ 30 mmHg (at rest, after Valsalva manoeuvre, or exercise).
- International guidelines (European Society of Cardiology); and the American Heart Association and American College of Cardiology (AHA/ACC) (Ommen et al, 2020): The resubmission stated that in these guidelines, obstruction is defined as a peak LVOT gradient of ≥ 30 mmHg. The AHA/ACC (2020) guidelines state that the presence of peak LVOT gradient of ≥ 30 mmHg is considered to be indicative of obstruction, with resting or provoked gradients ≥ 50 mmHg generally considered a threshold for septal reduction therapy (SRT) in those patients with drug-refractory symptoms. The European Society of Cardiology guidelines (2014) provide a protocol for assessment and treatment of LVOT obstruction (Figure 3), where exercise stress echocardiography is recommended in symptomatic patients if bedside manoeuvres fail to induce LVOT ≥ 50 mmHg. The European Society of Cardiology guidelines (2014) also provide recommendations for SRT, where the threshold of a resting or maximum provoked LVOT gradient of ≥ 50 mmHg is recommended. The ESC agreed with the submission that current guidelines indicate that a peak LVOT gradient of ≥ 30 mmHg indicates obstruction, nevertheless noted that the eligibility criteria of the key clinical trial required a peak LVOT gradient of ≥ 50 mmHg and this plausibly reflected a higher risk population.
 - Eligibility criteria for EXPLORER-HCM: The resubmission stated that the inclusion criteria for EXPLORER-HCM (the pivotal evidence presented for mavacamten in HCM) were for a baseline peak LVOT gradient at rest or on provocation (Valsalva or post-exercise) at diagnosis to be ≥ 50 mmHg. However, the study recruited a 'significant proportion' of patients with a baseline LVOT < 50 mmHg. Evidence presented in the resubmission indicated that approximately 13% of patients recruited to EXPLORER-HCM had a Valsalva LVOT gradient between 30 mmHg and 50 mmHg at baseline. The ESC considered this argument was not persuasive as the eligibility criteria for the trial specifically required that at least one measure of baseline LVOT gradient (rest or on provocation) should measure ≥ 50 mmHg. Hence, the ESC considered that this did not address its concerns with regards to reducing the restriction criteria to a peak LVOT gradient of ≥ 30 mmHg.

- The resubmission argued there is likely to be an extremely small number of patients who have an LVOT gradient at rest between 30 mmHg and 50 mmHg based on Maron et al., (2006)¹. From this study, a small proportion of patients (n=11; 11/320=3.4%) had an LVOT gradient between 30 mmHg and 50 mmHg. Maron et al., (2006) was a prospective population based epidemiological study of patients with HCM conducted at three referral centres in the USA (two centres) and Italy (one centre) between July 2003 and November 2004. The evaluation considered that epidemiologic estimates from Maron et al (2006) were not a reliable basis for translation to the Australian setting, given that the study contained a small sample size (N=320) for HCM which is a relatively common disorder. As above, the ESC considered that this did not address its concerns with regards to reducing the restriction criteria to a peak LVOT gradient of ≥ 30 mmHg. The ESC agreed that any patients who have a rest or provokable gradient > 50 mmHg be eligible under the proposed restriction, but disagreed with the submission and the PSCR which would allow patients with a rest or provokable gradient of 30-50 mmHg be eligible when they would not have been eligible under the clinical trial eligibility criteria.
 - The resubmission proposed an RSA as a means of addressing the potential uncertainty associated with use in patients with an LVOT lower than 50 mmHg. The ESC advised that RSAs are not created for the purpose of broadening restrictions of medicines to patients for whom there is minimal clinical evidence.
- 3.5 The ESC noted the PSCR appeared to argue that the peak LVOT criterion at screening in the EXPLORER-HCM trial was included to account for echocardiogram variations in LVOT gradient measures that occur between sites and the core lab to reduce screen failure at trial enrolment. The ESC did not consider the issue was satisfactorily addressed in the PSCR. The ESC remained concerned that the requested PBS criterion for LVOT of ≥ 30 mmHg would create potential for extension of access to patients with lower gradient in whom effectiveness has not been adequately demonstrated by EXPLORER-HCM.
- 3.6 The resubmission stated that the sponsor is considering opening a Patient Access Program (PAP) for approximately 3 months to provide access to mavacamten for patients with symptomatic obstructive HCM prior to PBS reimbursement. A grandfathering restriction for such a patient population was not requested as part of the November 2022 submission (para. 6.63, mavacamten, PBAC Public Summary Document (PSD), November 2022 PBAC meeting). The proposed grandfathering listing in this resubmission is intended for both patients who are still titrating to their individualised dose and those who have established their maintenance dose of

¹ Maron, M. S., Olivotto, I., Zenovich, A. G., Link, M. S., Pandian, N. G., Kuvin, J. T., Nistri, S., Cecchi, F., Udelson, J. E., & Maron, B. J. (2006). Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation*, 114(21), 2232–2239. <https://doi.org/10.1161/CIRCULATIONAHA.106.644682>

mavacamten (2.5 mg, 5 mg, 10 mg or 15 mg). The evaluation considered that it was unclear whether patients in the PAP would be eligible for initiation of treatment under the proposed initiation restriction. For example, the proposed grandfathering restriction does not state the peak LVOT, which increases uncertainty in the financial estimates with regard to the number of patients who might access treatment via the PAP. The PSCR clarified that the eligibility criteria for the PAP will align with the initiation or all treatment phase restriction of mavacamten upon its PBS listing to ensure patients can easily transition from non-PBS to PBS-subsidised treatment. The ESC considered this appropriate.

- 3.7 Mavacamten is proposed for long term use. The resubmission did not address the ESC and the PBAC's view that a stopping rule remained an important consideration, especially given that almost two-thirds (63.4%) of patients treated with mavacamten failed to meet the primary endpoint of the EXPLORER-HCM trial and half (49%) of patients treated with mavacamten remained symptomatic after 30 weeks of treatment (NYHA II/III) (para. 3.8 & 3.9, mavacamten, Public Summary Document, November 2022 PBAC meeting). Previously, the ESC considered that criteria based on NYHA or the Kansas City Cardiomyopathy Questionnaire (KCCQ) and potentially LVOT gradient could also be considered as criteria for discontinuation of mavacamten treatment (para. 3.8, mavacamten, Public Summary Document, November 2022 PBAC meeting). The ESC reiterated its concern that the lack of a stopping rule could result in a large number of patients who did not respond to mavacamten remaining on treatment indefinitely. The pre-PBAC response argued that regular 12-week echocardiogram monitoring would enable the treating physician to closely monitor a patient's ongoing clinical response to mavacamten and that they would be the best placed to determine whether treatment discontinuation was required. The sponsor further argued that clinician judgement for assessing discontinuation has been accepted across a number of PBS listed cardiovascular medications and that it appeared apparent that no stopping rule applies to recently listed cardiovascular medicines. The pre-PBAC response also argued that the proportion of patients experiencing improvements of at least 1 NYHA class increased over time (Week 120: 75.9%, Week 132: 81.4%, Week 144: 89.5%, Week 156: 100%) and therefore considered it inappropriate to propose a stopping rule as there is evidence that patients may achieve benefit over time. The PBAC remained concerned that patients may remain on mavacamten without an adequate clinical response indefinitely. The PBAC noted the comment in the pre-PBAC response that the proportion of patients experiencing improvements increased over time, but also noted that this data was based on a very small number of patients and was open label and considered the data unreliable for decision making. The PBAC remained concerned that clinician discretion left open the possibility that patients who did not respond may remain on mavacamten indefinitely.
- 3.8 The ESC noted that there are a number of patients with phenotypic manifestations of HCM, especially among older patients with asymmetric left ventricular hypertrophy

(LVH) secondary to hypertension, but do not have the genotype of HCM and under the proposed restriction there is likely to be a substantial risk of leakage to patients without HCM. However, the ESC did not consider that it would be appropriate for the restriction to specify that HCM must be confirmed by genetic testing for multiple reasons, including that this was not required by the clinical trial, would add significant cost and that current genetic testing is limited to only 20 of the most common genes associated with HCM. Rather, the ESC felt that this concern would be best met with an RSA and a stopping or discontinuation rule. Further to this, the ESC considered that the proposed restriction should include a definition of familial HCM (e.g. first degree relatives).

- 3.9 The ESC noted that the submission positioned mavacamten as a second line add on treatment where patients remain symptomatic despite treatment with a CCB or BB. However, the ESC considered that it may be more appropriate to position mavacamten for patients who remained symptomatic after previously receiving trials of both a CCB and a BB (unless intolerant/contraindicated to one or both) rather than just after a trial of either a BB or CCB. The pre-PBAC response maintained that the appropriate positioning of mavacamten is as a second-line adjunctive therapy for patients with symptomatic obstructive HCM and argued that the positioning of mavacamten as a third-line therapy would not align with the clinical evidence presented in the EXPLORER-HCM trial, where the majority of patients had prior exposure to either a BB or a CCB, not necessarily sequential trialling both.

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

4 Population and disease

- 4.1 HCM is a relatively common (1/200-400) genetic disorder that, in most studies, is the most common cause of sudden cardiac death in young adults (including athletes). It is characterised by (usually asymmetric) hypertrophy of the heart muscle (often the left ventricle (LV)), with normal left ventricular ejection fraction (LVEF) but impaired relaxation of the LV. Approximately two-thirds of individuals with HCM have LVOT obstruction (at rest or on provocation) and are said to have 'obstructive HCM'. The extent of obstruction, referred to as the gradient, can show significant variability.
- 4.2 The initial treatment of HCM is usually a non-vasodilating BB titrated to maximal tolerated dose. When BB are contraindicated or ineffective, a non-dihydropyridine CCB, most commonly verapamil, is used. These treatments are non-specific to HCM and are not effective in all patients. If symptoms persist, septal reduction therapy is considered. Previously the PBAC and ESC noted that there was minimal clinical usage of disopyramide (paras. 5.2 and 7.5, mavacamten, Public Summary Document, November 2022 PBAC meeting). Disopyramide was deleted from the ARTG in 14-Dec-22.
- 4.3 One of the hallmarks of HCM is an excess of myosin-actin cross bridges formed in the sarcomere. Mavacamten is a selective, allosteric, and reversible cardiac myosin

inhibitor, developed to target the underlying pathophysiology of obstructive HCM (exaggerated myosin-actin interaction). It reduces the number of myosin heads that can enter power-generating states, normalising the systolic and diastolic cross bridge formation.

5 Comparator

- 5.1 The resubmission nominated current SOC, which is a BB or non-dihydropyridine CCB, as the main comparator. The PBAC previously accepted SOC (BB or CCB) to be the appropriate comparator (para. 7.5, mavacamten, Public Summary Document, November 2022 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician provided a statement supporting the listing of mavacamten for obstructive HCM. The clinician stated that the medical therapy options (i.e., BBs, CCBs, and disopyramide) for patients with obstructive HCM are only partially effective at relieving symptoms and noted that septal reduction therapies are costly, invasive, and not widely available in Australia. The statement provided by the clinician highlighted the clinical benefits of mavacamten, as reported in the EXPLORER-HCM and VALOR-HCM clinical trials. The clinician noted that based on these trials, treatment with mavacamten was associated with improved exercise capacity, LVOT obstruction, NYHA functional class, and health status when compared to standard of care. The clinician considered that these clinical improvements would flow-on to improve patient's daily lives and their ability to work. The clinician noted that a clinical response may take as long as 6 months and that a stopping rule may lead to premature exclusion of patients who may take several months to respond to treatment. The clinician also emphasised that clinical response to a newly introduced therapy is multifaceted and should not be based on a single clinical parameter. For these reasons, the clinician considered that clinician discretion for whether a patient should continue/discontinue mavacamten was appropriate.
- 6.2 The PBAC particularly noted the emphasis of the hearing on the time to patient response, the multifaceted assessment of obstructive HCM and the suggestion for clinical discretion for continuation of therapy. Other aspects of contention with the restriction such as the qualifying LVOT gradient were not addressed.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from health care professionals (HCPs) (3), individuals (5) and consumer organisations (2) via the Consumer Comments facility on the PBS website.

- 6.4 The comments from HCPs noted the limitations of medical therapy options and invasive medical procedures (alcohol septal ablation or surgical myectomy) and described the clinical and quality of life benefits associated with mavacamten observed in clinical trials. The input also noted the adverse effects associated with mavacamten treatment, in particular the risk of reduced left ventricular ejection fraction and emphasised the need for regular echocardiograms and ongoing monitoring during treatment. The input also raised concerns that regular echocardiograms may not be covered by Medicare and lead to considerable out-of-pocket costs for patients.
- 6.5 Input from individuals who would like access to mavacamten to treat their own health condition, described the burden of disease associated with obstructive HCM, including difficulties to work full-time, complete routine daily tasks and participate in activities with family and friends. Individuals described that their reduced physical functioning had a significant impact on their and the family and friends' emotional and mental well-being. Individuals noted the lack of available treatment options for obstructive HCM, and expressed a need for new therapies to both relieve symptoms and improve the underlying cause of the disease. The input also noted the side effects and perceived a need for regular clinical support and monitoring. One individual noted the positive comments made by members in a HCM support group that reported improved symptoms and an ability to return to daily activities and the anxiety felt when experiencing side effects due to a fear they may be required to discontinue treatment.
- 6.6 The PBAC noted the advice received from 2 organisations, hearts4heart and Cardiomyopathy Association of Australia (CMAA). Hearts4hearts reaffirmed their previous advice (September 2022) that despite the availability of a number of therapeutic options for patients with obstructive HCM, there remained a clinical need for patients not suitable for procedures and/or non-respondent to current medical therapies. Hearts4heart considered that mavacamten was associated with significant improvements to quality of life and clinical outcomes for symptomatic patients living with HCM and noted that it was considered to be generally well tolerated. Hearts4heart reiterated that mavacamten had potential to significantly improve the daily lives of patients, noting that patients report feeling less symptoms and are more able to work and engage in leisure activities and exercise when taking mavacamten.
- 6.7 The CMAA expressed support for the listing of mavacamten for patients with obstructive HCM, noting that despite the availability of a number of medical therapies, many patients remain burdened by symptomatic disease. The CMAA considered surgery (myectomy) a reliable option for patients suffering from symptomatic disease, however noted that it was invasive, associated with complications and a recovery time. The CMAA noted that both patients and clinicians considered mavacamten was likely to reduce symptoms and prevent surgery. The CMAA also noted that patients report a willingness to undergo regular echocardiograms for the potential for symptom relief and the avoidance of surgery.

6.8 The PBAC considered the comments reflected the clinical evidence available.

Clinical trials

6.9 The resubmission was based on the same trials presented in the November 2022 submission. The key head-to-head trial was EXPLORER-HCM (N=251) comparing mavacamten (\pm BB/CCB) to placebo (\pm BB/CCB). The duration of follow-up from EXPLORER-HCM was 38 weeks. The details and results from EXPLORER-HCM remain unchanged from those presented in the November 2022 submission.

6.10 Updated evidence for two supporting trials was presented in the resubmission:

- MAVA-LTE (EXPLORER-LTE cohort) (N=231), which is the extension study for patients enrolled in EXPLORER-HCM. The resubmission presented interim results for the EXPLORER-LTE cohort for a data cut-off 31 May 2022; and
- VALOR-HCM (N=112), a Phase III, randomised, double-blind, placebo-controlled trial comparing mavacamten to placebo in a severe symptomatic population of patients with obstructive HCM who had been referred for SRTs. VALOR-HCM was presented as supporting evidence and partially evaluated, as part of the November 2022 submission on the basis that only a PowerPoint presentation of the results (up to week 16) was provided at that time. The resubmission has provided the interim CSR (dated June 2022, data cut-off 07 February 2022) and three publications (Cremer 2022, Desai 2022a, Desai 2022b) for VALOR-HCM. Results are presented up to week 32. VALOR-HCM is currently ongoing and is expected to be completed 10 June 2024.

6.11 No new data were provided in the resubmission for the two additional non-comparative supportive trials (PIONEER-HCM, and PIONEER-OLE) presented in the November 2022 submission. The PSCR provided updated results for PIONEER-OLE². PIONEER-HCM included a small number of patients (N=21); patients from PIONEER-HCM progressing to the open-label study, PIONEER-OLE (N=13). The PIONEER-HCM and the PIONEER-OLE studies were very small non-comparative studies. In the PIONEER-HCM study only cohort B was relevant for the resubmission's proposed patient population.

6.12 Details of the trials presented in the resubmission are provided in Table 3.

² Masri et al. 2023. Long-term safety and efficacy of mavacamten in patients with symptomatic obstructive hypertrophic cardiomyopathy: updated results from the PIONEER-OLE study. Poster 1066-07. American College of Cardiology (ACC)/World Congress of Cardiology (WCC).

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
EXPLORER-HCM (NCT03470545)	EXPLORER-HCM CSR. A Phase III, Randomised, Double-Blind, Placebo-Controlled Clinical Study to evaluate mavacamten in adults with symptomatic obstructive HCM. Olivotto et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial Spertus et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial Elliott. The end of the beginning for drug therapy in obstructive hypertrophic cardiomyopathy with EXPLORER-HCM. Burstein Waldman C, Owens A. A plain language summary of the EXPLORER-HCM study: mavacamten for obstructive hypertrophic cardiomyopathy. Hegde et al. Effect of Mavacamten on Echocardiographic Features in Symptomatic Patients With Obstructive Hypertrophic Cardiomyopathy. Xie et al. Assessing health-related quality-of-life in patients with symptomatic obstructive hypertrophic cardiomyopathy: EQ-5D-based utilities in the EXPLORER-HCM trial.	2020 <i>Lancet</i> . 2020 Sep 12;396(10253):759-769. <i>Lancet</i> . 2021 June 26;397(10293):2467-2475 <i>Cardiovasc Res</i> . 2020 Nov 1;116(13):e175-e178. <i>Future Cardiol</i> . 2021 Oct;17(7):1269-1275 <i>J Am Coll Cardiol</i> . 2021 Dec 21;78(25):2518-2532. <i>J Med Econ</i> . 2022 Jan-Dec;25(1):51-58.
	Wheeler, M. T., Olivotto, I., Elliott, P. M., et al. Effects of Mavacamten on Measures of Cardiopulmonary Exercise Testing Beyond Peak Oxygen Consumption: A Secondary Analysis of the EXPLORER-HCM Randomized Trial.	<i>JAMA Cardiology</i> , March 2023, 8(3):240-24.
MAVA-LTE (NCT03723655)	EXPLORER-LTE interim report. A Long-term Safety Extension Study of Mavacamten (MYK-461) in Adults with Hypertrophic Cardiomyopathy Who Have completed EXPLORER-HCM (MYK-461-005) (MYK-461-007; MAVA-LTE).	2022
EXPLORER-HCM and MAVA-LTE	Wheeler MT, Jacoby D, Elliott PM, Saberi S, Hegde SM, Lakdawala NK, Myers J, Sehnert AJ, Edelberg JM, Li W, Olivotto I. Effect of beta-blocker therapy on the response to mavacamten in patients with symptomatic obstructive hypertrophic cardiomyopathy.	<i>Eur J Heart Fail</i> . 2023 Feb;25(2):260-270.
VALOR-HCM (NCT04349072)	VALOR-HCM CSR. A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy who are Eligible for Septal Reduction Therapy. Desai, M. Y., Owens, A., Geske, J. B., et al. 2022. Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy. Desai, M. Y., Owens, A. T., Geske, J. B., et al. 2022. Dose-Blinded Myosin Inhibition in Patients with Obstructive HCM Referred for Septal Reduction Therapy: Outcomes Through 32-Weeks.	2022 <i>Journal of the American College of Cardiology</i> . 2022; 80:95-108 <i>Circulation</i> . 2023 Mar 14;147(11):850-863.

Source: Table 16, p47-49 of the November 2022 submission; Table 13 p37 of the resubmission.

HCM = hypertrophic cardiomyopathy; LTE = long term extension; MAVA = mavacamten.

Blue shading represents information previously considered by the PBAC.

6.13 The key features of the trials presented in the resubmission are summarised in Table 4. The risk of bias for EXPLORER-HCM was previously considered low. The evaluation considered that the risk of bias for VALOR-HCM was low. The evaluation considered that the risk of bias for MAVA-LTE (EXPLORER-HCM cohort) was low to unclear as the

results for the interim analysis were not yet mature; the results provided were subject to attrition bias. MAVA-LTE is ongoing and is due to be completed by April 2026.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Mavacamten (± BB/CCB) vs placebo (± BB/CCB)						
EXPLORER-HCM	251	MC, R, DB 38 weeks	Low	Symptomatic obstructive HCM NYHA II-III and LVOT ≥ 50 mmHg	Primary composite effectiveness outcome ^a ; Secondary/exploratory. <ul style="list-style-type: none"> post-exercise LVOT peak gradient; pVO₂; Change in NYHA class; and KCCQ-23 CSS. 	NYHA class
MAVA-LTE (EXPLORER-LTE cohort) ^b	231	LTE, blinded to study dose 252 weeks (ongoing) ^c	Low- unclear		Primary: safety; Secondary/exploratory <ul style="list-style-type: none"> Change in NYHA class. 	NYHA class ^d
VALOR-HCM	112	MC, R, DB 32 weeks ^e	Low	Symptomatic obstructive HCM NYHA II-IV and LVOT ≥ 50 mmHg referred for SRT	Primary composite effectiveness outcome; Patients (%) proceeding with SRT or who remained guideline-eligible after 16 weeks treatment. Secondary/exploratory: <ul style="list-style-type: none"> Post-exercise LVOT peak gradient; Change in NYHA class; KCCQ-23 CSS. 	Not used

Source: Compiled during the evaluation using Table 32, p 74 and Table 33, p74-75 of the November 2022 submission; MAVA-LTE, NCT03723655 (URL: <https://clinicaltrials.gov/ct2/show/NCT03723655>), MAVA-LTE CSR table of contents; VALOR-HCM CSR Table 2-1 pp30-31. For design and duration, see Table 26, p 67 and Table 29, p70 of the November 2022 submission; Table 20 p44, p43 of the resubmission; MAVA-LTE, Wheeler 2023 p262; VALOR-CSR p32, p35, Table 6.1.1-1 p75, Table 6.2.1-1 p77.

AE = adverse event; BB= beta-blocker; CCB= calcium channel blocker; DB = double blind; HCM = hypertrophic cardiomyopathy; KCCQ-23 CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LTE = long term extension; LVOT = left ventricular outflow tract; MC = multi-centre; NYHA = New York Health Association; R = randomised; SAE = serious adverse event; SRT = Septal Reduction Therapy.

^a proportion of patients who achieved either an improvement of ≥1.5 mL/kg/min in pVO₂ as determined by cardiopulmonary exercise testing and a reduction ≥1 NYHA class OR an improvement of ≥3.0 mL/kg/in in pVO₂ with no worsening in NYHA class;

^b MAVA-LTE is the long-term extension study for patients enrolled in EXPLORER-HCM.

^c MAVA-LTE is ongoing with estimated completion date 16 April 2026. The mean duration of treatment is: 110.3 weeks. Results from interim CSR reported for data cut-off, 31 May 2022.

^d Transition probabilities for BB/CCB monotherapy between Week 30 of EXPLORER-HCM and Week 46, which was the start of the extension study MAVA-LTE, were also applied to the economic model as a sensitivity analysis in the modelled evaluation.

^e VALOR-HCM long term extension is still ongoing (duration of treatment expected to be 128 weeks). Results for outcomes have been presented to Week 32.

Blue shading represents information previously considered by the PBAC.

6.14 During the November 2022 evaluation, it was observed that the PBAC had not previously considered peak oxygen consumption (pVO₂) as a surrogate outcome for quality of life (QoL) measures and survival and that the submission did not systematically justify pVO₂ as a surrogate outcome as per Appendix 5 of the PBAC guidelines (version 5.0). The ESC was previously satisfied that pVO₂ was a reasonable and reproducible measure of exercise capacity and hence potential functional benefit, although not of a mortality benefit in this population (para. 6.15, mavacamten, Public Summary Document, November 2022 PBAC meeting).

6.15 The resubmission stated that a targeted literature search was conducted which identified seven publications (Fiuzat et al., 2020³; Karapolat et al., 2008⁴; Sarcomeric Human Cardiomyopathy Registry (SHaRe), Tompkins et al., 2018⁵; Bennett et al., 2002⁶; SHaRe, Lakdawala et al., 2022⁷; Gallagher et al., 2019⁸; Wang et al., 2022⁹) to support the primary composite surrogate outcome to predict deaths and hospitalisations. Abstracts from SHaRe (Tompkins et al., 2018; Lakdawala et al., 2022) were presented in the November 2022 submission. Limited information is provided in the abstracts and the full papers do not appear to have been published (these could not be located during the evaluation). Two of the publications identified (Gallagher et al., 2019; Wang et al., 2022) are new in the resubmission. Limited information is provided in Wang et al., (2022), which is published as an abstract. Gallagher et al., (2019) observed NYHA class were significantly correlated with health-related QoL; however, within each NYHA class, there was a wide spread of health-related QoL scores. The study was conducted in a convenience sample within an urban population at a single tertiary centre, which limits generalisability of the results. The relationship between NYHA class and mortality was not assessed by Gallagher et al., (2019).

³ Fiuzat, M., Lowy, N., Stockbridge, N., Sbolli, M., Latta, F., Lindenfeld, J., Lewis, E. F., Abraham, W. T., Teerlink, J., Walsh, M., Heidenreich, P., Bozkurt, B., Starling, R. C., Solomon, S., Felker, G. M., Butler, J., Yancy, C., Stevenson, L. W., O'Connor, C., ... McMurray, J. (2020). Endpoints in Heart Failure Drug Development: History and Future. *JACC Heart Fail*, 8(6), 429–440. <https://doi.org/10.1016/j.jchf.2019.12.011>

⁴ Karapolat, H., Eyigor, S., Durmaz, B., Nalbantgil, S., Yagdi, T., & Zoghi, M. (2008). The effect of functional performance, respiratory function and osteopenia on the quality of life after heart transplantation. *Int J Cardiol*, 124(3), 381–383. <https://doi.org/10.1016/j.ijcard.2006.12.053>

⁵ Tompkins, J. D. v, Day, S. M., Jacoby, D. L., Colan, S. D., Olivotto, I., Ashley, E. A., Sehnert, A. J., Ho, C. Y., & null, null. (2018). Abstract 14251: Peak Oxygen Consumption is an Independent Predictor of Survival and Outcomes in Obstructive and Non-Obstructive Hypertrophic Cardiomyopathy (HCM) Patients: Results From the International Sarcomeric Human Cardiomyopathies Registry (SHaRe). *Circulation*, 138(Suppl_1), A14251–A14251. https://doi.org/10.1161/circ.138.suppl_1.14251

⁶ Bennett, J. A., Riegel, B., Bittner, V., & Nichols, J. (2002). Validity and reliability of the NYHA classes for measuring research outcomes in patients with cardiac disease. *Heart Lung*, 31(4), 262–270. <https://doi.org/10.1067/mhl.2002.124554>

⁷ Lakdawala, N., Saberi, S., Day, S., Ingles, J., Semsarian, C., Olivotto, I., Ho, C., Fine, J., Xu, Y., Sutton, M., Xie, J., & Wang, Y. (2022). New York Heart Association Functional Class And Mortality In Obstructive Hypertrophic Cardiomyopathy. *Journal of Cardiac Failure*, 28(5, Supplement), S37–S38. <https://doi.org/https://doi.org/10.1016/j.cardfail.2022.03.101>

⁸ Gallagher, A. M., Lucas, R., & Cowie, M. R. (2019). Assessing health-related quality of life in heart failure patients attending an outpatient clinic: a pragmatic approach. *ESC Heart Fail*, 6(1), 3–9. <https://doi.org/10.1002/ehf2.12363>

⁹ Wang, Y., Li, S., Gao, W., Jiang, J., Wei, Z., Sandler, B., Li, X., & Zema, C. (2022). OUTCOMES BY NEW YORK HEART ASSOCIATION CLASS AMONG PATIENTS WITH OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY. *Journal of the American College of Cardiology*, 79(9_Supplement), 238. [https://doi.org/10.1016/S0735-1097\(22\)01229-3](https://doi.org/10.1016/S0735-1097(22)01229-3)

Comparative effectiveness

- 6.16 The key clinical evidence from EXPLORER-HCM is summarised in Table 5, Table 6 and Table 7. Results from EXPLORER-HCM are unchanged from the November 2022 submission.
- 6.17 The primary outcome was a composite functional endpoint, that measured clinical response by 30 weeks, defined as either: (1) an improvement of at least 1.5 mL/kg/min in pVO₂ and improvement of one or more New York Health Association (NYHA class) (component 1); or, (2) an improvement of at least 3.0 mL/kg/min in pVO₂ with no worsening in NYHA class, unless otherwise denoted (component 2). Over twice as many patients in the mavacamten arm of the EXPLORER-HCM met the primary endpoint as in the placebo arm (36.6% vs 17.2%, OR=2.74, 95% CI 1.51, 5.45). The PBAC previously considered mavacamten provided only a moderate improvement in outcomes, with 63.4% of mavacamten patients failing to meet the primary endpoint (i.e., a composite of functional endpoints); 35% did not improve NYHA class; and 49% remained NYHA II/III (i.e. symptomatic) (para. 7.6, mavacamten Public Summary Document, November 2022 PBAC meeting).

Table 5: EXPLORER-HCM, Primary composite endpoint at week 30 (ITT population)

	Mavacamten (N = 123)	Placebo (N = 128)	Mavacamten vs. Placebo RD (95% CI) ^a	Stratified Analysis ^c OR (95% CI)	Unstratified Analysis ^d OR (95% CI)
Achieved Composite Functional Endpoint ^b , n (%)	45 (36.6)	22 (17.2)	19.4 (8.67, 30.13)	2.74 (1.51, 5.45) p = 0.0005	2.78 (1.54, 5.00) p = 0.0005
Patients (%) with ≥ 3 mL/kg/min in pVO ₂ and improvement ≥ 1 NYHA class ^e	25 (20.3)	10 (7.8)	12.5 (4.02, 21.01)	3.01 (1.38, 6.57)	NR

Source: Table 43, p101 of the November 2022 submission.

CI = confidence interval; ITT = intention to treat; N = total participants in group; NR = not reported; NYHA = New York Heart Association; RD = risk difference; OR = odds ratio; pVO₂ = peak oxygen consumption

^a The 95% CIs of the response differences between mavacamten and placebo groups are based on normal approximation.

^b The composite functional endpoint was defined as either: Type 1) an improvement of at least 1.5 mL/kg/min in pVO₂ and improvement of one or more NYHA class or Type 2) an improvement of at least 3.0 mL/kg/min in pVO₂ with no worsening in NYHA class, unless otherwise denoted. Missing NYHA class at Week 30 was imputed using available NYHA class at Week 26. After the imputation, the patients whose response status at Week 30 was still missing were classified as non-responders.

^c The analysis was stratified on NYHA class, beta-blocker use, and exercise type (based on IXRS). Odds ratio was estimated using Cochran-Mantel-Haenszel method. Odds ratio > 1 indicates better outcome when comparing to placebo. P-value and 95% CI were derived using the exact method.

^d Unstratified analysis is performed as sensitivity analysis. P-value and 95% CI is derived from Pearson's Chi-square test.

^e These are the most stringent pVO₂ and NYHA class components of the composite functional endpoint and do not reflect either component 1 or component 2 of the composite functional endpoint.

^f Calculated during the November 2022 evaluation, using Stata.

Blue shading represents information previously considered by the PBAC.

6.18 At baseline, all patients in EXPLORER-HCM were of NYHA class II or III. In the mavacamten arm, 65% of patients experienced at least one NYHA class improvement from baseline to Week 30, whereas in the placebo arm, 31.1% of patients had at least one NYHA class improvement (Table 6).

Table 6: Change from baseline to week 30 in NYHA class

NYHA Class	Mavacamten (N = 123)			Placebo (N = 128)		
	Class II n (%)	Class III n (%)	Total n (%)	Class II n (%)	Class III n (%)	Total n (%)
Baseline	88 (71.5)	35 (28.5)	123 (100.0)	95 (74.2)	33 (25.8)	128 (100.0)
Week 30, n (%)						
Class I	52 (42.3)	9 (7.3)	61 (49.6)	24 (18.8)	3 (2.3)	27 (21.1)
Class II	33 (26.8)	19 (15.4)	52 (42.3)	61 (47.7)	13 (10.2)	74 (57.8)
Class III	1 (0.8)	7 (5.7)	8 (6.5)	9 (7.0)	16 (12.5)	25 (19.5)
Missing	2 (1.6)	0	2 (1.6)	1 (0.8)	1 (0.8)	2 (1.6)

Source: Table 47, p106 of the November 2022 submission

NYHA = New York Heart Association

Baseline is defined as the last non-missing measurement prior to the first dose of study drug.

All assessments are summarised by analysis visits per statistical analysis plan (SAP).

Missing NYHA class at Week 30 was imputed using available NYHA at Week 26.

Blue shading represents information previously considered by the PBAC.

6.19 Quality of life data were collected in EXPLORER-HCM using the EQ-5D-5L. Response rates were similar between treatment arms. During the 30-week treatment period, the main EQ-5D-5L scores remained close to the baseline values for both treatment

groups, with no statistically significant differences observed between the mavacamten arm and the placebo arm (Table 7). The PBAC noted that the moderate improvements observed in the functional outcomes of the trial (see paragraph 6.17) did not flow through to a difference in quality of life measures.

Table 7: EXPLORER-HCM, median (range) EQ-5D-5L results by visit (ITT)

Visit	Mavacamten (n=123)		Placebo (n=128)		Mavacamten vs Placebo difference
Baseline	(n=101)	0.877 (0.20,1.00)	(n=98)	0.843 (0.31,1.00)	0.034
Week 6	(n=106)	0.932 (-0.37,1.00)	(n=104)	0.847 (0.44,1.00)	0.085
Week 12	(n=109)	0.943 (0.51,1.00)	(n=110)	0.903 (-0.04,1.00)	0.040
Week 18	(n=110)	0.940 (0.25,1.00)	(n=119)	0.932 (0.07,1.00)	0.008
Week 30	(n=111)	0.943 (0.45,1.00)	(n=113)	0.883 (0.12,1.00)	0.060
Week 38	(n=78)	0.829 (0.33,1.00)	(n=81)	0.883 (0.08,1.00)	-0.054

Source: Table 59, p124 of the submission.

EQ-5D-5L = EuroQol five dimension, five levels; ITT = intention to treat; n = number of patients who provided responses

Blue shading represents information previously considered by the PBAC.

6.20 The key clinical evidence from MAVA-LTE (EXPLORER-LTE cohort) is summarised in Table 8.

Table 8: MAVA-LTE (EXPLORER-LTE Cohort), NYHA function class change from baseline

	Week 108 N=101	Week 120 N=79	Week 132 N=43	Week 144 N=19	Week 156 N=3
Improve by 1 class, n (%)	60 (59.4)	52 (65.8)	30 (69.8)	14 (73.7)	1 (33.3)
Improve by 2 classes, n (%)	12 (11.9)	8 (10.1)	5 (11.6)	3 (15.8)	2 (66.7)
Remain the same, n (%)	29 (28.7)	18 (22.8)	8 (18.6)	2 (10.5)	0
Worsen by 1 class, n (%)	0	1 (1.3)	0	0	0
Worsen by 2 classes, n (%)	0	0	0	0	0
Patients with at least 1 class of improvement, n (%) (95% CI)	72 (71.3) (61.4, 79.9)	60 (75.9) (65.0, 84.9)	35 (81.4) (66.6, 91.6)	17 (89.5) (66.9, 98.7)	3 (100) (29.2, 100)

Source: Table 17, pp40-41 of the resubmission.

CI = confidence interval; N = total participants in group; NYHA = New York Heart Association.

6.21 The proportion of patients with improvements in NYHA class increased at each timepoint from Week 48 to Week 156. From Week 132, no patients were classified as NYHA class III or IV and no patients experienced worsening of NYHA class compared with baseline. Noting the reduced sample size over time, the proportion of patients experiencing improvements of ≥ 1 NYHA class increased over time (Week 120: 75.9%, Week 132: 81.4%, Week 144: 89.5%, Week 156: 100%). Data for MAVA-LTE are immature; there are only 19 (8.2%) patients informing the analysis at Week 144 and 3 (1.3%) informing the analysis at Week 156. The ESC considered that this data may have been affected by attrition bias.

6.22 The resubmission stated that the results from EXPLORER-LTE up to Week 156 are consistent with those reported in EXPLORER-HCM. Treatment with mavacamten resulted in sustained improvements in NYHA class from Week 48 to Week 156, suggesting there is no diminishing effect with prolonged treatment. The evaluation considered that this was reasonable given the results up to Week 132; results thereafter reflect very small sample sizes and cannot be interpreted with confidence.

- 6.23 The primary outcome in VALOR-HCM was the proportion of patients proceeding with SRT or who remained guideline-eligible for SRT after 16 weeks treatment. At Week 16, 76.8% of patients in the placebo group met the primary outcome (need for SRT among eligible patients) compared with 17.9% in the mavacamten group. The mean difference between mavacamten and placebo in the primary SRT composite outcome at Week 16 was 58.9% (95% CI: 44.0% to 73.9%). The ESC noted that despite 43 patients (76.8%) in the placebo group meeting the primary outcome (either through decision to proceed to SRT or remained guideline eligible for SRT) only 2 patients (3.6%) elected to proceed with SRT.
- 6.24 The change in NYHA functional class was a secondary outcome in VALOR-HCM. A higher proportion of patients receiving treatment with mavacamten experienced an improvement of at least 1 class from baseline to Week 16 in NYHA class compared with placebo (62.5% vs 21.4% respectively; mean difference of 41.1%; 95% CI, 24.5 to 57.7, $p < 0.0001$). The proportion of patients with an improvement of at least 1 NYHA class from baseline increased to 90.6% by Week 32 among patients receiving treatment with mavacamten from the start of the study.

Comparative harms

- 6.25 A summary of the comparative harms associated with mavacamten versus placebo from EXPLORER-HCM and MAVA-LTE (EXPLORER-LTE cohort) is presented in Table 9.

Table 9: Overall summary of AEs in EXPLORER-HCM and MAVA-LTE (EXPLORER-LTE cohort)

	EXPLORER-HCM		MAVA-LTE
	Mavacamten (N = 123)	Placebo (N = 128)	EXPLORER-LTE cohort (N = 231)
Total Number of TEAEs	536	495	1323
Patients with any:			
TEAEs, n (%)	108 (87.8)	104 (81.3)	219 (94.8)
Serious TEAEs	14 (11.4)	12 (9.4)	[NR]
Drug-related TEAEs	19 (15.4)	18 (14.1)	45 (19.5)
Drug-related serious TEAEs	0	1 (0.8)	6 (2.6)
Treatment interruption due to TEAEs	3 (2.4)	6 (4.7)	20 (8.7)
Treatment discontinuation due to TEAEs ^a	2 (1.6)	0	11 (4.8)
Study discontinuation due to TEAEs	2 (1.6)	1 (0.8)	8 (3.5)
TEAEs leading to death	0	1 (0.8)	4 (1.7)

Source: Table 61, p127 of the November 2022 submission; Table 19 p43, of the resubmission.

AE = adverse event; CV = cardiovascular; LVEF = left ventricular ejection fraction; N = number of participants in the group; NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Blue shading represents information previously considered by the PBAC.

- 6.26 In MAVA-LTE (EXPLORER-HCM cohort), 94.8% of patients reported at least one treatment-emergent adverse event (TEAE) (mild, 34.6%; moderate, 45.5%; severe, 13.0%). Serious adverse events (SAE) were observed in 47 patients (20.3%). Four patients experienced a TEAE leading to death (events: bacterial endocarditis; cardiac arrest; acute myocardial infarction; and intracerebral haemorrhage). The resubmission stated that, while there was a slightly higher rate of TEAEs observed in MAVA-LTE (EXPLORER-HCM cohort), mavacamten was generally well tolerated and no new safety signals were observed. A higher percentage of TEAEs was observed over

the longer-term (data cut-off: 31 May 2022) in MAVA-LTE (EXPLORER-LTE cohort) (94.8%) compared to after 30 weeks of treatment in EXPLORER-HCM (87.8%).

- 6.27 In VALOR-HCM, the most common AEs of any grade experienced among patients receiving treatment with mavacamten after 32 weeks included fatigue (n=7; 12.5%), palpitations (n=6; 10.7%), atrial fibrillation (n=5; 8.9%), nausea (n=5; 8.9%) and dizziness (8.9%). For patients in the placebo crossover group receiving mavacamten after Week 16, the most common AEs included dizziness (n=5; 9.6%), palpitations (n=3; 5.8%), atrial fibrillation (n=3; 5.8%) and headache (n=3; 5.8%) after 16 weeks of treatment with mavacamten.
- 6.28 The ESC recalled its previous advice that the primary adverse event of concern was reduced LVEF. The ESC had previously noted this was infrequently observed and reversible with temporary treatment cessation (para. 6.28, mavacamten, Public Summary Document, November 2022 PBAC meeting). However, given patients would require monitoring with echocardiography every 3 months after dose stabilisation to reduce the risk of left ventricular systolic dysfunction developing, the additional patient burden of frequent monitoring and barriers to access requires consideration before prescribing.

Benefits/harms

- 6.29 A summary of the comparative benefits and harms from the key trial EXPLORER-HCM for mavacamten versus placebo is presented in Table 10.

Table 10: Summary of comparative benefits and harms for mavacamten versus placebo

Outcome	Mavacamten n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)	
				Mavacamten	Placebo		
Benefits							
Dichotomous outcomes							
Achieved composite functional endpoint ^a	45/123	22/128	2.13 (1.36, 3.32)	36.6	17.2	19.4 (8.67, 30.13)	
Proportion of patients with ≥ 3 mL/kg/min in pVO ₂ and improvement ≥ 1 NYHA class ^b	25/123	10/128	2.60 (1.30, 5.19)	20.3	7.8	12.5 (4.02, 21.01)	
Continuous outcomes: change from baseline to Week 30							
	Mavacamten			Placebo			Mean difference Mavacamten vs. placebo (95% CI)
	N	Mean Δ baseline LVOT (mmHg)	SD	N	Mean Δ baseline LVOT (mmHg)	SD	
Post exercise LVOT peak gradient (mmHg)	117	-47	40.3	122	-0.30	29.6	-35 (-43.2, -28.1)

Peak oxygen consumption (pVO ₂)	120	1.4	3.12	125	-0.05	3.02	1.4 (0.59, 2.12)
Categorical outcomes: NYHA class: proportion reduced from baseline to Week 30							
	Mavacamten		Placebo		RR (95%CI)		
Downgraded ≥ 1 class	80/123 (65.0%)		40/128 (31.3%)		2.08 (1.56, 2.78)		
Harms							
	Mavacamten n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)	
				Mavacamten	Placebo		
Adverse event between baseline and Week 30							
Patients with ≥ 1 TEAE	108/123	101/128	1.11 (1.00, 1.24)	87.8	78.9	8.9 (-0.27, 18.07)	
Patients with serious TEAE	14/123	12/128	1.21 (0.58, 2.52)	11.4	9.4	2.00 (-5.53, 9.54)	

Source: Table 43 p101, Table 44 p102, Table 45 p103, Table 47 p106, Table 61 p127, Table 62, pp127-128 of the November 2022 submission.

CI = confidence interval; LVOT = left ventricular outflow tract; n = number of participants with event; N = total participants in group; NYHA = New York Heart Association, pVO₂ = peak oxygen consumption; RD = risk difference; RR = risk ratio; SD = standard deviation; TEAE = treatment-emergent adverse event.

Blue indicates statistically significant results.

^a The composite functional endpoint was defined as either: Type 1) an improvement of at least 1.5 mL/kg/min in pVO₂ and improvement of one or more NYHA class, or Type 2) an improvement of at least 3.0 mL/kg/min in pVO₂ with no worsening in NYHA class, unless otherwise denoted. Missing NYHA class at Week 30 was imputed using available NYHA class at Week 26. After the imputation, the patients whose response status at Week 30 was still missing were classified as non-responders.

^b These are the most stringent pVO₂ and NYHA class components of the composite functional endpoint combined and do not reflect either component 1 or component 2 of the composite functional endpoint.

Blue shading represents information previously considered by the PBAC.

6.30 On the basis of evidence presented by the submission from EXPLORER-HCM, for every 100 patients with symptomatic obstructive HCM treated with mavacamten ± BB/CCB in comparison with placebo ± BB/CCB over a 30 Week period:

- Approximately 19 additional patients will meet the composite functional endpoint. The endpoint was defined as either: (1) a small (at least 1.5 mL/kg/min in pVO₂) improvement in the maximum amount of oxygen that an individual can utilise during intense or maximal exercise combined with an increase in the ability to do physical activities (shown by an improvement of NYHA class), or: (2) a larger (at least 3.0 mL/kg/min in pVO₂) improvement in the maximum amount of oxygen that an individual can utilise during intense or maximal exercise, with no worsening in physical activities.
- Approximately 13 additional patients will achieve a significant improvement in the maximum amount of oxygen that an individual can utilise during intense or maximal exercise (at least 3.0 mL/kg/min in pVO₂) and an increase in the ability to do physical activities (shown by an improvement of NYHA class).
- Approximately 34 additional patients would have a measurable improvement in the ability to do physical activities (shown by an improvement of NYHA class).

Clinical claim

- 6.31 The resubmission described mavacamten ± BB/CCB as superior in terms of effectiveness and inferior in terms of safety compared to SOC alone (BB/CCB).
- 6.32 The therapeutic conclusion for comparative effectiveness presented in the resubmission was reasonable for the management of symptomatic outcomes pertaining to obstructive HCM. The PBAC previously noted that EXPLORER-HCM was a small trial (N=251) with a short duration of comparative follow up (30 weeks); and symptomatic/functional endpoints were only reported. It was noted that the goal of therapy was symptomatic improvement, preferably through reduction in disease severity (para. 7.6 mavacamten, Public Summary Document, November 2022 PBAC meeting).
- 6.33 The therapeutic conclusion for comparative safety revised in the resubmission was reasonable. The PBAC previously considered that the primary adverse event of concern was reduced LVEF and noted that the long-term consequences of treatment compared with SOC were unknown (para. 7.7, mavacamten, Public Summary Document, November 2022 PBAC meeting). The ESC recalled its previous consideration of the increased risk of reduced LVEF associated with mavacamten and noted the additional 4–8 echocardiograms per year that would be required to monitor patients prescribed mavacamten.
- 6.34 At the November 2022 meeting, the PBAC considered it is likely that mavacamten ± BB/CCB provided at least a short-term, moderate clinical benefit over standard of care (BB/CCB), but the longer-term clinical benefit and safety and the impact on other patient-relevant clinical endpoints such as hospitalisations or mortality was unknown (para. 7.1, mavacamten, Public Summary Document, November 2022 PBAC meeting). The PBAC considered that the effect mavacamten has on other patient relevant outcomes such as hospitalisation and mortality cannot be practically evaluated in trials in HCM patients because these events are rare. Furthermore, although obstruction is a risk predictor for sudden cardiac death in HCM, there is no evidence that these deaths would be reduced with mavacamten and hence mavacamten is therefore not expected to provide mortality benefits (para. 7.6, mavacamten, Public Summary Document, November 2022 PBAC meeting). While there was evidence for mavacamten use in the longer-term, up to 132 weeks, evidence for relevant events of interest, such as hospitalisations and mortality, was lacking. The PBAC also noted the absence of any supportive quality of life data.
- 6.35 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.36 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.37 In November 2022, the PBAC considered that the estimated cost per quality adjusted life year (QALY) gained for mavacamten + BB/CCB compared with BB/CCB of \$35,000 to < \$45,000/QALY gained for the submission’s base case was likely to be underestimated (para. 7.1 & 7.9, mavacamten, Public Summary Document (PSD), November 2022 PBAC meeting). The PBAC considered that the incremental cost-effectiveness ratio (ICER) was highly sensitive to a number of the modelled assumptions and that a respecified base case should include the following:

- A 10-year time horizon;
- Truncation at 30 weeks in both arms (at duration of comparative follow-up);
- No mortality benefit for mavacamten; and
- Amended inputs for: cardiovascular hospitalisation rates and costs, SRT costs, disopyramide benefits, and discontinuation rates.

6.38 The ESC noted that the resubmission did not implement several of the PBAC’s recommended changes for the respecified base case. The resubmission did not amend the time horizon to 10 years, it maintained differential points for the truncation of observed data related to change in NYHA functional class, and it retained an assumed mortality benefit for mavacamten. The resubmission did not amend the cardiovascular hospitalisation rates and estimated cost for SRT. The key components of the revised economic model and how it differed from that in November 2022 are summarised in Table 11.

Table 11: Summary of model structure, key inputs and rationale

Component	November 2022 model	Resubmission model
Treatments	Mavacamten + BB/CCB versus BB/CCB alone	Unchanged.
Time horizon	25 years in the model base case versus 38 weeks in the key trial EXPLORER-HCM (30-week treatment period + 8-week follow-up)	Revised to 20 years (PBAC advice: 10 years) .
Outcomes	Number of responders, life years gained, quality-adjusted life years gained	Unchanged.
Methods used to generate results	Markov state transition model	Unchanged.
Health states	Four health states: NYHA class I, NYHA class II, NYHA class III/IV, death	Unchanged.
Cycle length	Short-term (within 30 weeks, i.e. the treatment period in the trial): consistent with the visit schedule for efficacy measures in EXPLORER-HCM (either 2 weeks or 4 weeks) Long-term (beyond 30 weeks): 4 weeks	Unchanged.
Transition probabilities	Transition probabilities among NYHA health states were estimated based on the trial data from EXPLORER-HCM up to 30 weeks for mavacamten + BB/CCB and up to 46 weeks for SOC (i.e. BB/CCB).	Unchanged for mavacamten + BB/CCB arm. Truncation point revised from 46 weeks to 38 weeks for SOC arm (PBAC advice: revise to 30 weeks for both arms). Sensitivity was presented truncation time point of 30 weeks for both arms.

Public Summary Document – July 2023 PBAC Meeting

Component	November 2022 model	Resubmission model
Extrapolation method	<p>After the trial data truncation time point, the model assumed that patients receiving mavacamten + BB/CCB or BB/CCB alone experienced no further NYHA class change except for underlying natural disease progression. The estimate of the disease progression rate in patients treated with BB/CCB was sourced from an external study by Maron et al (2016). The rate of natural disease progression for mavacamten + BB/CCB was estimated by applying a relative difference of 50.85% (derived from EXPLORER-HCM) to the assumed disease progression rate for BB/CCB.</p> <p>The submission assumed that patients would remain on their initial treatment with mavacamten + BB/CCB or BB/CCB alone for the first 30 weeks. Thereafter, patients have a probability of discontinuing mavacamten treatment, due to AEs or lack of efficacy, and receive subsequent therapy with BB/CCB, disopyramide + BB/CCB or SRT + BB/CCB. Patients not responding to BB/CCB monotherapy have a probability of receiving subsequent treatments (i.e. disopyramide + BB/CCB or and SRT + BB/CCB). The proportion of patients who would receive subsequent therapies and the market share of subsequent therapies were estimated based on EXPLORER-HCM and expert opinion from an Advisory Board.</p> <p>The submission assumed that patients treated with disopyramide + BB/CCB experienced no improvement in NYHA class but followed the natural disease progression. The transition probabilities among NYHA class health states in patients receiving SRT + BB/CCB were sourced from a Ukrainian study (Knyshov et al., 2013).</p>	<p>Unchanged.</p> <p>Assumption unchanged for patients discontinuing mavacamten treated due to lack of efficacy (ESC Advice: stronger justification needed for long-term discontinuation)</p> <p>Changes made in resubmission model:</p> <ul style="list-style-type: none"> Disopyramide was removed as a subsequent therapy from the model's structure. Assumed market share for disopyramide were shifted to BB/CCB for the mavacamten arm and to SRT + BB/CCB for the SOC arm. Discontinuation rates revised for patients discontinuing mavacamten due to SAEs: after 30 weeks from 1.6% to 5.0%; Patients discontinuing due to SAEs annually was revised from 2.8% to 8.53% (calculation applied based on week 30 discontinuation rate). <p>Unchanged.</p>

Public Summary Document – July 2023 PBAC Meeting

Component	November 2022 model	Resubmission model
	<p>The mortality rate in NYHA class I patients was the general population mortality rate obtained from ABS Life Tables. Hazard ratios were used to reflect the excess mortality associated with NYHA class II and NYHA class III/IV, based on adjusted analyses using the Sarcomeric Human Cardiomyopathy Registry.</p> <p>98% of the incremental QALYs and 77% of the incremental costs occurred in the extrapolated period (i.e. from 30 weeks to 25 years).</p>	<p>Unchanged.</p> <p>Technical reports for analyses were not provided; validity of the adjusted HR results could not be validated or reliably assessed. (PBAC advice: remove mortality benefits) 98% of the incremental QALYs and 72% of the incremental costs occurred in the extrapolated period (i.e., from 30 weeks to 20 years).</p>
Health related quality of life	<p>Utilities were NYHA functional class dependent, regardless of the treatments the patients received. No AE-associated utility decrements were included in the economic model. Health state utility values were estimated based on the EQ-5D data from EXPLORER-HCM.</p> <p>NYHA class I: 0.909; NYHA class II: 0.827; NYHA class III/IV: 0.730</p>	Unchanged.
Costs	<p>Drug costs were estimated based on the proposed or published PBS prices.</p> <p>The health care resource use associated with treatment monitoring and management of disease was sourced from the mavacamten PI and expert opinion from the Advisory Board. MBS Schedule fees were used to cost related medical services. The cost of cardiovascular hospitalisation for disease management and the cost for SRT were estimated as the weighted average of selected AR-DRGs items.</p> <p>The terminal care cost was sourced from an Australian study which reported the hospital inpatient costs among older people in their last year of life.</p>	<p>Effective DPMQ for mavacamten reduced from \$█ to \$█.</p> <p>Costs unchanged:</p> <ul style="list-style-type: none"> • SRT: \$55,911 (PBAC advice: amend as cost due to SRT was overestimated). • CV hospitalisation rates: NYHA II, 0.38 and NYHA III/IV, 1.0 (PBAC advice: amend input). <p>Costs revised:</p> <ul style="list-style-type: none"> • CV hospitalisation cost: reduced from \$27,780 to \$12,486. • Costs of other treatments (metoprolol, atenolol, bisoprolol, diltiazem, verapamil) and monitoring costs. <p>Unchanged.</p>

Source: Table 81, p189 and Sections 3.4 to 3.6, pp191-217 of the November 2022 submission; Table 39, pp72-74, and Section 3.1 to 3.6 of the resubmission

ABS = Australian Bureau of Statistics; AE = adverse events; AR-DRGs = Australian Refined Diagnosis Related Groups; BB = beta-blocker; CCB = calcium channel blocker; CV = cardiovascular; DPMQ = dispensed price for maximum quantity; EQ-5D = EuroQol 5-Dimensions; HCM = hypertrophic cardiomyopathy; HR = hazard ratio; MBS = Medicare Benefits Schedule; NYHA = New York Heart Association; PBAC = Pharmaceutical Benefits Advisory Committee; PI = Product Information; SOC = standard of care; SRT = septal reduction therapy.

6.39 A summary of the changes requested by the PBAC for a respecified base case and components of the revised model are provided in Table 12. Changes pertaining to the main sources of uncertainty as noted by the PBAC and the ESC from that in November 2022 are discussed in the paragraphs below and in Table 12.

Table 12: Summary of model structure, key inputs and rationale

Parameter	JUL 2023	NOV 2022	Comments (PBAC from Nov 2022)
Effective AEMP	\$█	\$█	Price reduction of █% off last price offered.
Time horizon	20 years	25 years	PBAC: 10 years – not implemented Resubmission: time horizon of 20 years based on long-term data from MAVA-LTE (EXPLORER-LTE cohort) (submission)
Truncation point MAVA + BB/CCB SOC (BB/CCB)	30 weeks 38 weeks	30 weeks 46 weeks	PBAC: 30 weeks in both arms – not implemented Resubmission: truncation point at 38 weeks, which is the end of EXPLORER-HCM follow up (submission).
Mortality benefit	Mortality benefit modelled	Mortality benefit modelled	PBAC: Remove mortality benefit – not implemented Resubmission: Maintained mortality benefit. Based on Jacobsen et al (2023) and Zampieri et al (2022) (of the submission).
CV hospitalisation costs	\$12,486	\$27,780	PBAC: revised base case should amend cost of hospitalisation – implemented; and remove differences in hospitalisations – not implemented. Resubmission: revised costs based on AIHW (2022). Rates have not been revised and was based on Advisory Board survey (of 9 cardiologists) (submission).
CV hospitalisation rates	NYHA II, 0.38; and NYHA III/IV, 1.0 applied each cycle	NYHA II, 0.38; and NYHA III/IV, 1.0 applied each cycle	
Septal reduction therapy (SRT) costs	SRT costs \$55,911	SRT costs \$55,911	PBAC: SRT costs are overestimated, favouring mavacamten – not implemented. Submission: Maintained costs based on Sun et al. (2022) (submission).
Disopyramide benefits	Disopyramide removed from model structure.	Benefits not included. Costs were included.	PBAC: Including costs of subsequent therapies but no benefit was not appropriate. Resubmission: removed from model based on disopyramide being delisted by the TGA 14-Dec-22 and Advisory Board (Attachment 14).
Discontinuation rates due to SAEs	Base case: short term 5%	Base case: short term 1.6%	PBAC: Discontinuation rates may be higher in clinical practice – partially implemented. Resubmission: Revised the proportion of patients discontinuing treatment due to SAE at week 30 in resubmission. The long-term discontinuation rate due to SAE are calculated from the short-term discontinuation rate. Assumption for discontinuation due to lack of response were not revised. No justification was provided.
Discontinuation due to lack of response	Discontinue if no NYHA class improvement	Discontinue if no NYHA class improvement	

Source : Compiled during the evaluation using Table 81, p189 and Sections 3.4 to 3.6, pp191-217 of the November 2022 submission; and using information provided in p80, pp83-84, pp88-89, and Section 3.6, pp92-99 of the resubmission. AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; BBs= beta-blockers; CCBs= calcium channel blockers; CV = cardiovascular; ESC = Economic Sub Committee; HCM = hypertrophic cardiomyopathy; LTE = long term extension; MAVA = mavacamten; PBAC = Pharmaceutical Benefits Advisory Committee; SAE = serious adverse event; SRT = Septal reduction therapy; TGA = Therapeutic Goods Administration.

- 6.40 The PBAC previously considered a respecified base case should include a 10-year time horizon, because the duration of the clinical data available from EXPLORER-HCM was inadequate to inform the modelled long-term estimates (para. 7.8, mavacamten, Public Summary Document, November 2022 PBAC meeting).
- 6.41 The resubmission stated that the reduction in time horizon to 20 years (from 25 years in the November 2022 submission) is to acknowledge the uncertainty in the economic

model. The resubmission justified the selection of the 20-year time horizon (as opposed to the 10 years recommended by the PBAC) stating that longer-term efficacy data have been provided from MAVA-LTE (EXPLORER-HCM cohort) out to 156 weeks. MAVA-LTE is still ongoing; only three (3/231=1.3%) patients have completed week 156 - by week 108 (~2.1 years), data had been collected from 101 (43.7%) patients (MAVA-LTE CSR Table B.1). EXPLORER-HCM provides up to 30-weeks of comparative clinical data for mavacamten. The PSCR stated that while the sponsor considered the 25-year time horizon, utilised in the original submission, to be appropriate, it had been revised downward to acknowledge uncertainty. The PSCR argued that a time horizon of 10 years was unreasonable, noting the different time horizons that had been recently accepted by the PBAC for cardiovascular indications, varying from 10 years (vericiguat; with short duration of pivotal trial median follow-up and older patient cohort at baseline) to 30 years (dapagliflozin; older cohort at baseline and a short median duration of pivotal trial follow-up). The PSCR also argued that the EXPLORER-LTE data (with median follow-up data of 26.84 months) was used in the resubmission to confirm the ongoing treatment effect of mavacamten and demonstrated that the assumption in the base case of the model that patients do not improve their NYHA functional class after week 30 may be conservative.

- 6.42 The ESC acknowledged that a longer time horizon than 10 years would normally be appropriate for a treatment such as mavacamten and considered that the proposed 20 year time horizon could be justified, noting that this increased uncertainty over the extrapolated period. The ESC considered that the uncertainty associated with the long extrapolation in the economic model beyond the short time frame of the EXPLORER-HCM trial would need to be mitigated in an RSA.
- 6.43 The PBAC noted previously that the model is sensitive to the assumed truncation point; where different data truncation points (30 weeks for mavacamten + BB/CCB arm and 46 weeks for the comparator) were applied to each arm of the model for data related to change in NYHA functional class. The PBAC previously advised that data should be truncated at 30 weeks in both arms (para. 7.9, mavacamten, Public Summary Document, November 2022 PBAC meeting). Despite this advice, the resubmission continued to apply different truncation points to each arm in the model, discussed below.
- 6.44 Short-term transition probabilities for the change in NYHA functional class were based on data from EXPLORER-HCM. Probabilities for short-term transitions were applied as follows:
- Mavacamten + BB/CCB: Transition probabilities were derived up to week 30, i.e. the end of treatment period in EXPLORER-HCM. This remains unchanged from the November 2022 submission.
 - Placebo + BB/CCB: Transition probabilities were derived up to week 38 i.e., end of the follow up period in EXPLORER-HCM. The resubmission reasoned that the NYHA class distribution among patients in the placebo ± BB/CCB arm of the

EXPLORER-HCM demonstrated a favourable improvement until about Week 22, despite the fact that most (88%) of these patients had already received BB/CCB prior to the trial and their treatment did not change upon participating in the trial. Patients in the BB/CCB monotherapy arm did not receive study treatment (i.e., placebo) after week 30, but were still blinded to their original randomisation, and were still part of the trial/about to commence the MAVA-LTE study. The impact of using observed transition probabilities up to either week 30 or up to week 46 of the EXPLORER-HCM trial to inform short-term transition probabilities for the BB/CCB monotherapy arm was assessed in sensitivity analyses.

- 6.45 The ESC agreed with the evaluation that the justifications provided by the resubmission do not adequately support retaining the truncation point for BB/CCB at 38 weeks (beyond that of mavacamten); noting that the improvements in NYHA class appear to have ceased at week 22. As discussed in the November 2022 commentary, the purpose of the double-blind, placebo-controlled trial design of EXPLORER-HCM was to control for non-specific effects beyond the action of mavacamten, such as the placebo effect and Hawthorne effect, which existed in both treatment arms. The inclusion of additional data after the end of double-blinded treatments (beyond week 30) in the placebo group means that these non-specific effects have been controlled for in the placebo arm but not in the mavacamten arm. The pre-PBAC response acknowledged the ESC's advice that the truncation of observed data should occur at 30 weeks for both treatment arms and accepted this amendment to the base case.
- 6.46 The resubmission's economic model assumed different mortality rates based on patient NYHA class in each model cycle. This assumption was unchanged from the November 2022 submission's economic model, where an overall survival benefit associated with mavacamten over SOC was assumed, but not shown in the clinical data. The PBAC previously stated that a respecified base case for the economic evaluation should not include mortality benefits for mavacamten (para. 7.9, mavacamten, Public Summary Document, November 2022 PBAC meeting). The resubmission maintained that mortality should not be removed from the economic model based on two recent publications (Jacobsen et al., 2023¹⁰; Zampieri et al., 2022¹¹) that indicate that patients with HCM have increased mortality risk compared to the general population. The evaluation considered that although these papers present evidence which suggests increased mortality risk for HCM patients compared with the general population, these are retrospective non-randomised studies, with a

¹⁰ Jacobsen M-H B, Petersen J K, Modin D et al. Long-term mortality in patients with hypertrophic cardiomyopathy – A Danish nationwide study. *American Heart Journal Plus: Cardiology Research and Practice* 25(2023) 100244.

¹¹ Zampieri, M., Salvi, S., Fumagalli, C, et al., Clinical scenarios of HCM-related mortality: Relevance of age and stage of disease at presentation, *International Journal of Cardiology* (2023), <https://doi.org/10.1016/j.ijcard.2022.12.056>.

high-risk of bias and subject to serious limitations such as confounding of unmeasured prognostic factors. Methods for mitigating the risks associated with the differential distribution of known confounders because of non-random treatment allocation (such as matching and controlling for confounders in the analysis) cannot adjust for the differential distribution of unknown confounders (PBAC Guidelines v5.0). Both studies included patients from the years 2000 to 2007, where changes in clinical care, physician prescribing practice, diagnostic processes and treatments have evolved over time, limiting the applicability of the study results. The studies do not provide evidence of survival being impacted by mavacamten treatment or differences in NYHA class. Summaries of these studies are provided below:

- Jacobsen et al., (2023) was a matched cohort study, comparing mortality in a nationwide cohort of patients with HCM (N=1,197) (diagnosed between January 2007 to December 2018) with the general population in Denmark (N=3,404). Patients with HCM were matched to controls from the population (1:3) based on age, sex, selected comorbidities and date of HCM diagnosis. After adjusting for selected comorbidities and medications, a diagnosis with HCM was associated with an increased mortality rate (HR = 1.48 (95% CI: 1.18–1.84%, p = 0.001)) compared with matched controls. The annual mortality rate was 3% for patients with HCM compared with 2% among controls. Limitations of the study pertain to confounding due to differences in the characteristics of the cohorts in the matched analysis, which were not considered (including details on the degree of outflow tract obstruction, the specific causes of deaths, and predictors for these outcomes).
- Zampieri et al., (2022) was a retrospective cohort study that investigated the modes of death of patients with HCM who died between the years 2000 and 2020 (N=161). Of the 161 patients, 103 (64%) died of HCM-related causes, whereas 58 (36%) died of non-HCM-related causes. Patients who died of HCM-related causes were younger than those who died of non-HCM related causes. A key limitation in this study is that the analysis for deaths were based on a small number of patients (N=161) over a 20-year period. Over two decades, changes in technical development, diagnostic processes, risk stratification and treatments have occurred, which limits the applicability of the study results.

The PSCR maintained that it was appropriate to model an overall survival benefit associated with mavacamten over SOC based on NYHA class improvement. The PSCR acknowledged that Jacobsen et al., (2023) and Zampieri et al., (2022) do not provide specific evidence of survival being improved by mavacamten treatment or NYHA class, however argued that the studies provide justification that obstructive HCM increases mortality risk. The ESC noted excess mortality associated with NYHA class II and NYHA class III/IV, based on adjusted analyses using the Sarcomeric Human Cardiomyopathy Registry could not be validated during the evaluation, nor was there any new data presented to suggest that reducing NYHA class with mavacamten for patients with obstructive HCM reduces mortality. For this reason, the ESC considered the

- justification provided in the resubmission and PSCR did not adequately support a difference in mortality rates within the economic model.
- 6.47 At the November 2022 PBAC meeting, the PBAC noted that EXPLORER-HCM only reported on symptomatic/functional outcomes. Hospitalisation and mortality outcomes are not evaluated in trials of patients with HCM because those events are rare, and patients are expected to have a normal life expectancy. Furthermore, there is no evidence deaths would be reduced with mavacamten (para. 7.6, mavacamten, Public Summary Document, November 2022 PBAC meeting).
- 6.48 The differences in the number of deaths between the two treatment groups as an outcome of the model over the 20-year time horizon is presented in Table 13. The cumulative percentage of death avoided for mavacamten + BB/CCB versus BB/CCB alone increased over time, from 0.1% at Week 30 to 6.5% at Year 20. Applying changes as requested by the PBAC, including truncation of the observed data used in both arms at 30 weeks and removing mortality benefits (i.e., no specific NYHA risk associated with mortality) reduced the differences in mortality over the first year; the maximum difference between the arms is 0.3% after 10 years.

Table 13: Average cumulative probability of mortality^a per patient over time in the economic model

	July 2023 resubmission base case			PBAC respecified changes								
				Truncation both arms at 30 weeks			Truncation both arms 30 weeks; mortality removed			Truncation both arms 30 weeks; mortality removed; 10 years		
	ICER: \$ ¹			ICER: \$ ²			ICER: \$ ³			ICER: \$ ⁴		
	MAVA + BB/CCB	BB/CCB	Diff.	MAVA + BB/CCB	BB/CCB	Diff.	MAVA + BB/CCB	BB/CCB	Diff.	MAVA + BB/CCB	BB/CCB	Diff.
Week 30	0.4%	0.5%	-0.1%	0.4%	0.5%	-0.1%	0.3%	0.3%	0.0%	0.3%	0.3%	0.0%
Year 1	0.8%	0.9%	-0.1%	0.8%	0.9%	-0.1%	0.6%	0.6%	0.0%	0.6%	0.6%	0.0%
Year 5	4.9%	6.5%	-1.6%	5.0%	6.5%	-1.5%	3.8%	4.0%	-0.2%	3.8%	4.0%	-0.2%
Year 10	12.1%	15.2%	-3.1%	12.3%	15.2%	-2.9%	9.1%	9.4%	-0.3%	9.1%	9.4%	-0.3%
Year 15	22.9%	27.7%	-4.8%	23.5%	27.7%	-4.2%	16.9%	17.1%	-0.2%	16.9%	17.1%	-0.2%
Year 20	38.8%	45.3%	-6.5%	39.7%	45.3%	-5.6%	28.2%	28.4%	-0.2%	28.2%	28.4%	-0.2%

Source: Table compiled during the evaluation, based on the "Mavacamten obstructive HCM model resubmission_FINAL" Excel workbook, July 2023 resubmission;

BB = beta-blocker; CCB = calcium-channel blocker; Diff. = difference; ICER = incremental cost-effectiveness ratio; MAVAs = mavacamten; PBAC = Pharmaceutical Benefits Advisory Committee.

^a Cumulative deaths were derived from Cells T30:T39 and Cells AR52:AR369 in the 'MAVA' and 'Comparator' spreadsheets.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$55,000 to < \$75,000

³ \$95,000 to < \$115,000

⁴ \$115,000 to < \$135,000

6.49 The resubmission adopted changes related to hospitalisation costs as noted in the PBAC's specified base case (para. 6.51 & 7.9, mavacamten, Public Summary Document, November 2022 PBAC meeting). The revised costs of hospitalisation of \$12,485.69 presented in the resubmission was based on the AIHW (2015)¹² estimates. The resubmission modelled different hospitalisation rates depending on NYHA class despite PBAC previous consideration that a revised base case should remove differences in hospitalisations (para. 6.51, mavacamten, Public Summary Document, November 2022 PBAC meeting). The PSCR maintained that increased rates of hospitalisations would be incurred for patients with higher NYHA classes. The PSCR stated that the rates of hospitalisations were derived from an advisory board survey (2021) which it argued represented the best available information to inform the economic model. The PSCR also argued that Jacobsen et al 2023 and Zampieri et al 2022 provided further evidence of worsening disease (i.e. increasing NYHA functional class) with increased mortality and complications and made reference to two further studies (Osman et al 2023¹³; Charron et al 2023¹⁴) that it argued supported increased hospitalisation rates for patients with obstructive HCM. The ESC noted that there were no data to suggest that reducing NYHA class with mavacamten for patients with

¹² Australian Institute of Health and Welfare. Hospital Performance: Costs of acute admitted patients in public hospitals in 2011–12. 2015; Available from: <https://www.aihw.gov.au/reports/hospitals/hospital-performance-costs-acute-patients-2011-12/contents/key-findings>. [Accessed August 2022].

¹³ Osman F, Zema C, Hurst M et al. Long-term cardiovascular outcomes and events by New York Heart Association class in patients with obstructive hypertrophic cardiomyopathy in England. May 2023 ESC-HFA Presentation 60737.

¹⁴ Charron P, Zema C, Cotte F-E et al. Clinical burden of obstructive hypertrophic cardiomyopathy: insights from a nationwide study in France. May 2023 European Society of Cardiology – Heart Failure Association Presentation 60869.

obstructive HCM reduces hospitalisations. For this reason, the ESC considered the justification provided in the resubmission and PSCR did not support a difference in hospitalisation rates within the economic model. The pre-PBAC response maintained that it is reasonable and appropriate to assume hospitalisation rates increase with increased NYHA class, and argued that this assumption was supported by published evidence and expert advice from Australian clinicians. The pre-PBAC response considered data, to be presented at the American Heart Association 2023 conference (Wang et al 2023¹⁵), further supported an association between worsening NYHA class and increased health care resource utilisation. A total of 754 adults with obstructive HCM in the United States were included in the retrospective cohort study. The mean annual number of all-cause hospitalisations was reported to increase with higher index NYHA classes (class I = 0.3; class II = 1.0; class III = 1.6; class IV = 2.1 ± 2.8). The pre-PBAC response noted that these values were higher than the values assumed in the revised base case (class I = 0; class II = 0.38; class III/IV = 1). The PBAC respecified base case in Table 16 reduced the cardiovascular hospitalisation rate by half rather than remove it altogether.

- 6.50 At the November 2022 PBAC meeting, the PBAC noted that the ESC considered the cost of SRT was overestimated in the economic evaluation; and advised that SRT costs should be amended (para. 7.8 & 7.9, mavacamten, Public Summary Document, November 2022 PBAC meeting). Despite the PBAC's advice, the resubmission retained the cost of SRT as used in the November 2022 submission. The resubmission argued that costs of SRT were not overestimated as SRT costs are applied as a once-off hospital cost in the model, which is unlikely to occur in practice. Based on Sun et al., (2022)¹⁶ the resubmission asserted that patients require cardiac rehabilitation as well as additional follow-up visits to their clinicians in the months after surgery which was not costed in the economic model. The PSCR noted that both Sun et al (2022)¹⁷ and Nagueh et al (2021)¹⁸ provided evidence that after SRT (either septal ablation or myectomy), a significant proportion of patients require either an emergency department visit or readmission within 2 years of treatment, with some patients requiring a repeat procedure. The PSCR argued that these additional downstream costs had not been incorporated into the once-off cost for SRT and therefore the sponsor maintained that the cost used was reasonable and potentially conservative. The ESC advised that a more transparent approach to estimating and reporting on costs of SRT would be required to justify the current estimates. The pre-PBAC response

¹⁵ Wang Y, Gao W, Gao S et al. Healthcare resource utilization and costs associated with New York Heart Association functional class in patients with obstructive hypertrophic cardiomyopathy in the United States. Submitted abstract to AHA 2023

¹⁶ Sun, D. Schaff H. V., Van Houten, H. K., et al. (2022) Longitudinal Cost of Septal Myectomy Versus Alcohol Septal Ablation for Hypertrophic Cardiomyopathy. *Mayo Clin Proc.* 97(9), 1656-1663.

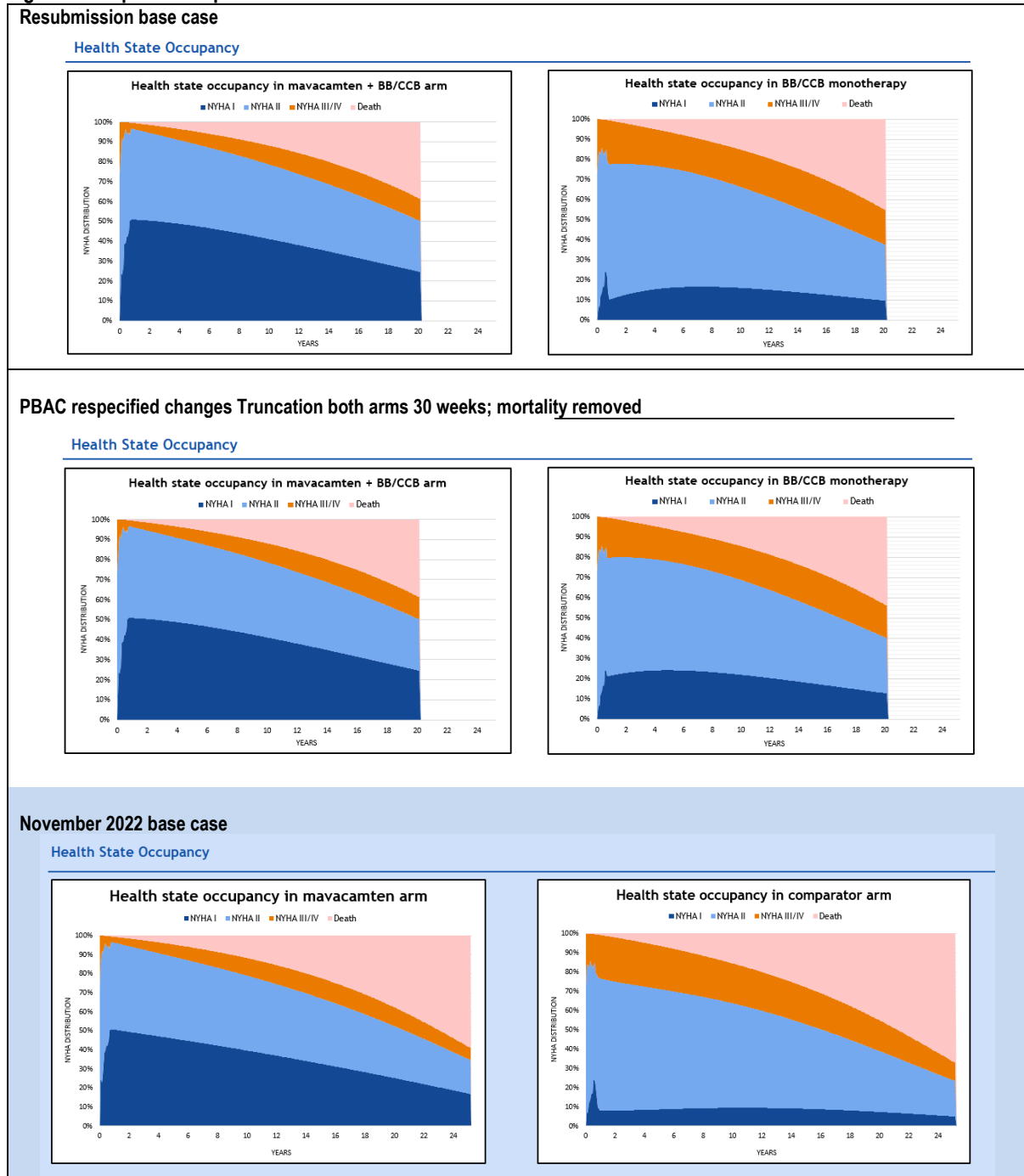
¹⁷ Sun, D. Schaff H. V., Van Houten, H. K., et al. (2022) Longitudinal Cost of Septal Myectomy Versus Alcohol Septal Ablation for Hypertrophic Cardiomyopathy. *Mayo Clin Proc.* 97(9), 1656-1663.

¹⁸ Nagueh, S. F., Groves B. M., Schwartz L et al (2011). Alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy. A multicenter North American registry. *J Am Coll Cardiol*, 58(22), 2322-2328.

maintained that the weighted costs for AR-DRG codes F05A/F05B for septal myectomy and F08/F08B/F08C for alcohol septal ablation were appropriate and likely to be conservative, as additional costs such as rehabilitation and ongoing complications had not been accounted for. The pre-PBAC response provided micro-costing in addition to the once-off procedure to support its assertion that the once-off cost applied was reasonable and likely to be underestimated. This micro-costing accounted for additional clinician visits, monitoring post-surgery, cardiac rehabilitation, emergency department visits and readmission due to complications, pacemaker insertion and repeat procedures required for some patients. The addition of on-going medical care resulted in an additional \$27,044 to the cost of a SRT procedure (\$55,895). The PBAC respecified base case in Table 16 uses the SRT rates from VALOR-HCM to address the impact of SRT in the model.

- 6.51 At the November 2022 meeting, the PBAC noted that the evaluation and the ESC considered a key issue was that discontinuation (even without a stopping rule) may be higher than modelled. The method used to model discontinuation due to lack of response was unchanged in the resubmission. The resubmission assumed that, if patients gained no benefits in terms of NYHA class whilst on mavacamten treatment, they would discontinue due to lack of response. This was inconsistent with the proposed PBS restriction, which does not include a stopping rule for mavacamten treatment. In EXPLORER-HCM, 63.4% of mavacamten patients did not achieve the primary composite endpoint and 48.8% of patients remained NYHA class II/III. The ESC previously considered a revised base case should include stronger justification for long-term treatment discontinuation. The PBAC previously considered that the respecified base case should include amended inputs for the discontinuation rates (para. 6.41 & 7.9, mavacamten, Public Summary Document, November 2022 PBAC meeting). No justification was provided in the resubmission for retaining the assumption relating to discontinuation due to lack of response. The resubmission revised inputs for the proportion of patients discontinuing mavacamten due to a serious adverse event (SAE) at week 30 from 1.6% to 5.0% and the ongoing annual discontinuation rate which was calculated as a function of the proportion of patients discontinuing mavacamten at week 30 (due to SAEs). This input was revised from 2.8% annually to 8.53% annually. However, the percentage of patients assumed to discontinue due to a lack of response at 30 weeks (no improvement in NYHA class) remained unchanged (NYHA I = 0%; NYHA II = 63.5%; NYHA = 100%). The PSCR argued that the increase to the percentages related to discontinuation due to SAEs are considered by the sponsor to account for both discontinuations associated with SAEs and a lack of response.
- 6.52 The distribution of patients in each health state over the model time horizon is provided in Figure 1. The impact on those distributions of applying changes requested by the PBAC, including truncation of observed data in both arms at 30 weeks and removing mortality (para. 7.9, mavacamten, Public Summary Document, November 2022 PBAC meeting), are also presented in Figure 1.

Figure 1: Proportion of patients in each health state over time



Source: Figure 53, p218 of the November 2022 submission; Figure 19, p100 of the resubmission; “Mavacamtan obstructive HCM model resubmission_FINAL” Excel workbook, July 2023 resubmission.

BB = beta-blocker; CCB = calcium channel blockers; NYHA = New York Heart Association.

Blue shading represents information previously considered by the PBAC.

6.53 A summary of the key drivers of the resubmission’s model is provided in Table 14.

Table 14: Key drivers of the model

Public Summary Document – July 2023 PBAC Meeting

Description	Method/Value	Impact Base case: \$ ¹ /QALY gained
Discontinuation of mavacamten therapy due to lack of efficacy at Week 30	Patients with no improvement in NYHA class from baseline	High, favoured mavacamten + BB/CCB. Assuming treatment discontinuation in patients with worsened NYHA class from base case at Week 30 increased the ICER to \$ ² /QALY gained.
Rates of cardiovascular hospitalisation	NYHA II, 0.38 NYHA III/IV, 1.0	High, favoured mavacamten + BB/CCB. Removing hospitalisation rates (i.e., reduced to zero) for patients with NYHA II to IV increased the ICER to \$ ² .
Efficacy of SRT + BB/CCB	Based on a Ukrainian study by Knyshov et al 2021	High, favoured mavacamten + BB/CCB. Use of sponsor's advisory board inputs increased the ICER to \$ ² /QALY gained.
Truncation time point in the BB/CCB arm	38 weeks	High, favoured mavacamten + BB/CCB. Use of comparative trial data up to 30 weeks for both arms increased the ICER to \$ ³ /QALY gained.
Time horizon	20 years	High, favoured mavacamten + BB/CCB. Use of a shorter time horizon of 10 years increased the ICER to \$ ³ /QALY gained
Mortality	NYHA class I: all-cause mortality, hazard ratio = 1.0 NYHA class II vs I: hazard ratio = 1.48 NYHA III/IV vs I: 3.17 Based on the SHaRe adjusted.	High, favoured mavacamten. All cause/general mortality not NYHA specific (1.0 across all NYHA classes) increase ICER to \$ ³ /QALY gained.

Source: Table compiled during the evaluation, based on the sensitivity analyses presented in the submission or conducted during the evaluation. Mortality sensitivity analyses performed during ESC evaluation.

BB = beta-blocker; CCB = calcium channel blocker; ICER = incremental cost-effectiveness ratio; NYHA = New York Heart Association; QALY = quality-adjusted life year; SHaRe = Sarcomeric Human Cardiomyopathy Registry; SRT = Septal Reduction Therapy.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$75,000 to < \$95,000

³ \$55,000 to < \$75,000

6.54 Results of the economic evaluation are presented in Table 15.

Table 15: Results of the stepped economic evaluation

Step and component	Resubmission July 2023			November 2022		
	MAVA + BB/CCB	BB/CCB	Increment	MAVA + BB/CCB	BB/CCB	Increment
Step 1: Comparative study data (30 weeks)						
Costs	\$█	\$3,662	\$ ^a	\$█	\$7,346	\$█
Responder ^b	36.6%	17.2%	19.4%	36.6%	17.2%	19.4%
Incremental cost per responder			\$ ¹			\$ ¹
Step 2: Study data transformed into LYG (30 weeks)						
Costs	\$█	\$3,662	\$ ^a	\$█	\$7,346	\$█
LYG	0.5734	0.5732	0.0002	0.5734	0.5732	0.0002
Incremental cost per LYG			\$█ ³			\$█ ³
Step 3: Applied utility values (30 weeks)						
Costs	\$█	\$3,662	\$ ^a	\$█	\$7,346	\$█
QALYs	0.49	0.47	0.02	0.49	0.47	0.02
Incremental cost per QALY gained			\$ ⁴			\$ ⁵
Step 4: Extrapolating to time horizon of 20 years			Extrapolating to time horizon of 25 years			
Costs	\$█	\$115,451	\$█	\$█	\$206,385	\$█
QALYs	9.86	9.14	0.72	10.61	9.64	0.98
Incremental cost per QALY gained			\$ ²			\$ ²

Source: Table 57, p102 of the resubmission.

BB = beta-blocker; CCB = calcium channel blocker; LYG = life year gained; MAVA = mavacamten; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life year.

^a Typo reported in resubmission as \$█ in Table 57, p102, however, modelled value is \$█.

^b Proportion of responders, according to the composite primary endpoint in EXPLORER-HCM. The composite endpoint was defined as either: 1) an improvement of at least 1.5 mL/kg/min in peak oxygen consumption (pVO₂) and improvement of one or more New York Heart Association (NYHA) class; or 2) an improvement of at least 3.0 mL/kg/min in pVO₂ with no worsening in NYHA class, unless otherwise denoted.

Blue shading represents information previously considered by the PBAC.

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$35,000 to < \$45,000

³ >\$1,055,000

⁴ \$455,000 to < \$555,000

⁵ \$555,000 to < \$655,000

6.55 The resubmission revised base case ICER was \$35,000 to < \$45,000/QALY. The ESC considered that it may be reasonable for the submission to adopt a 20 year time horizon, however a respecified base case should include all remaining PBAC recommended changes including: a data truncation at 30 weeks in both arms; removal of mortality benefits; removal of differences in hospitalisation rates; reduced cost of SRT; and increased discontinuation rates due to lack of response. A respecified ESC base case was estimated during ESC consideration and increased the ICER to \$155,000 to < \$255,000 per QALY gained (see the second final row in Table 16). The respecified base case does not include amendment to discontinuation rates, as it would likely require amendment to the model structure.

6.56 The PBAC noted the ESC respecified base case but offered an alternative revision as a way forward: time horizon of 20 years; data truncation at 30 weeks in both arms; removal of mortality benefits; halved cardiovascular hospitalisations rates; and the SRT rates from the VALOR-HCM trial. The PBAC noted this respecified base case ICER

increases to \$135,000 to < \$155,000 (see the final row in Table 16). The results of key sensitivity analyses are summarised in Table 16.

Table 16: Sensitivity analyses

Analyses	Incr. cost	Incr. QALY	ICER	% change to ICER
Base case of resubmission	\$█	0.72	\$█ ¹	-
November 2022 base case	\$█	0.98	\$█ ¹	-
Discount rate (base case: 5%)				
0%	0%	0%	0%	0%
3.5%	3.5%	3.5%	3.5%	3.5%
Time horizon (base case 20 years)				
1. 10 years	\$█	0.40	\$█ ²	+48.5%
Trial-based TP truncation time point (base case: 30 weeks for MAVA + BB/CCB and 38 weeks for BB/CCB)				
2. 30 weeks for both treatment arms	\$█	0.57	\$█ ²	+55.3%
Efficacy of SRT + BB/CCB (base case: Knyshov et al 2013)				
Advisory board inputs ^a	\$█	0.53	\$█ ³	+68.2%
Mortality HRs by NYHA class, compared with mortality in general population (base case: 1.0 for NYHA I, 1.48 for NYHA II and 3.17 for NYHA III/IV, based on the SHaRe adjusted)				
3. All cause/general mortality not NYHA specific (1.0 across all NYHA classes)	\$█	0.47	\$█ ²	+38.2%
4a. Cardiovascular (CV) hospitalisation rates (base case: NYHA II, 0.38 and NYHA III/IV, 1.00)				
4ai. Reduced to zero for NYHA II (i.e. 0.38 →0.00) ^a and NYHA III/IV patients (i.e. 1.00 →0.00) ^a	\$█	0.72	\$█ ³	+80.3%
4aii. Reduced by half for NYHA II (i.e. 0.38 →0.19) ^a and NYHA III/IV patients (i.e. 1.00 →0.50) ^a	\$█	0.72	\$█ ²	+40.2%
4b. Cost of hospitalisation associated with SRT (base case: \$55,895)				
4bi. Weighted unit cost reduced by 50% (i.e. \$27,947 per SRT-associated hospital admission) ^a	\$█	0.72	\$█ ⁴	+20.3%
4bii. Assuming market share of septal ablation therapy is 100% (i.e., myectomy, 0%, cost of septal ablation therapy \$37,106.20)	\$█	0.72	\$█ ⁴	+13.9%
4d. Discontinuation of mavacamten due to lack of response at Week 30 (base case: no improvement in NYHA class)				
4di. Worsening in NYHA class ^a	\$█	0.70	\$█ ³	+92.5%
4dii. LVOT gradient decreased: not able to implement in model.	-	-	-	-
Proportion of patients escalating to SRT after MAVA, base case: NYHA I, 4.0%; NYHA II, 8.7%; NYHA III/IV, 68.75%				
5. Patients (%) escalating from MAVA to SRT using VALOR-HCM (all NYHA classes: 3.6%)	\$█	0.70	\$█ ⁴	+7.0%
Multivariate analyses^a				
1. 10-year time horizon;	\$█	0.25	\$█ ⁵	+182.7%
2. TP truncation at 30 weeks both arms;				
3. Removal of mortality benefits.				

Public Summary Document – July 2023 PBAC Meeting

Analyses	Incr. cost	Incr. QALY	ICER	% change to ICER
1. • 10-year time horizon; 2. • TP truncation at 30 weeks both arms; 3. • Removal of mortality benefits. 4ai. • Assume CV hospitalisation rates reduced to zero 4bi. • Assume reduced weighted unit cost by half (i.e. \$27,947 per SRT-associated hospital admission).	\$█	0.25	\$█ ⁶	380.8%
1. • 20-year time horizon; 2. • TP truncation at 30 weeks both arms; 3. • Removal of mortality benefits.	\$█	0.37	\$█ ⁷	+123.9%
1. • 20-year time horizon; 2. • TP truncation at 30 weeks both arms; 3. • Removal of mortality benefits; 4ai. • Assume CV hospitalisation rates reduced to zero; 4bi. • Assume reduced weighted unit cost by half (i.e. \$27,947 per SRT-associated hospital admission); 5. • Patients (%) escalating from MAVA to SRT using VALOR-HCM.	\$█	0.36	\$█ ⁶	+310.4%
Respecified ESC base case 1. • 20-year time horizon; 2. • TP truncation at 30 weeks both arms; 3. • Removal of mortality benefits; 4ai. • Assume CV hospitalisation rates reduced to zero; 4bi. • Assume reduced weighted unit cost by half (i.e. \$27,947 per SRT-associated hospital admission).	\$█	0.37	\$█ ⁶	+298.1%
Respecified PBAC base case 1. • 20-year time horizon; 2. • TP truncation at 30 weeks both arms; 3. • Removal of mortality benefits; 4aii. • Reduced by half for CV rates NYHA II (i.e. 0.38 →0.19) ^a and NYHA III/IV patients (i.e. 1.00 →0.50) ^a 5. • Patients (%) escalating from MAVA to SRT using VALOR-HCM.	\$█	0.36	\$█ ⁸	+206.8%

Source: Table 64, pp108 of the resubmission; Mavacamten obstructive HCM model resubmission_FINAL, "Outcomes" spreadsheet.

BB = beta-blocker; CCB = calcium channel blocker; CV – cardiovascular; HR = hazard ratio; ICER = incremental cost-effectiveness; MAVA = mavacamten; QALY = quality-adjusted life year; NYHA = New York Heart Association; SAEs = serious adverse events; SRT = septal reduction therapy; TP = transition probability.

^a Sensitivity analyses performed during the evaluation or during ESC evaluation.

Blue shading indicates rows unchanged from the November 2022 submission.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

⁴ \$45,000 to < \$55,000

⁵ \$115,000 to < \$135,000

⁶ \$155,000 to < \$255,000

⁷ \$95,000 to < \$115,000

⁸ \$135,000 to < \$155,000

6.57 The key drivers of the economic model were consistent with a number of those identified during the November 2022 evaluation which are: time horizon, assumed point of truncation, mortality benefits, and costs for hospitalisation and SRT.

Drug cost/patient/year

6.58 A comparison of the drug cost for mavacamten estimated based on EXPLORER-HCM, in the economic evaluation and in the financial analysis is presented in Table 17. The cost of BB/CCB is not included in the table as patients in both treatment arms will receive BB/CCB therapy, either in combination with mavacamten or as monotherapy.

Table 17: Drug cost per patient for mavacamten

	Resubmission, July 2023			November 2022		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean dose	6.69 mg per day ^{a,b}	Not estimated ^b	Not estimated ^b	6.69 mg per day ^{a,b}	Not estimated ^b	Not estimated ^b
Cost per 28 capsules	\$█	\$█	\$█	\$█ ^c	\$█ ^c	\$█ ^c
Number of scripts per year	–	12.87 ^d (13.04 ^e)	12.73 ^f (13.04 ^e)	–	12.87 ^d (13.04 ^e)	12.73 ^f (13.04 ^e)
Cost/patient/year	–	\$█ ^d (\$█ ^e)	\$█ ^f (\$█ ^e)	–	\$█ ^d (\$█ ^e)	\$█ ^f (\$█ ^e)
Proportion of patients on treatment	At 30 weeks, 3.3% of patients in the MAVA arm of EXPLORER-HCM had discontinued treatment	Year 1: 100% ^g Year 2: 60.4% Year 3: 48.2% Year 4: 43.0% Year 5: 38.4% Year 6: 34.2%	Year 1: 100% ⁱ Year 2: 100% Year 3: 100% Year 4: 100% Year 5: 100% Year 6: 100%	At 30 weeks, 3.3% of patients in the MAVA arm of EXPLORER-HCM had discontinued treatment	Year 1: 100% ^g Year 2: 63.6% Year 3: 60.0% Year 4: 56.6% Year 5: 53.3% Year 6: 50.2%	Year 1: 100% ^h Year 2: 66.1% Year 3: 62.1% Year 4: 58.3% Year 5: 54.8% Year 6: 51.5%

Source: Table constructed during the evaluation, based on Table 9, p37 and Table 29, p70 of the November 2022 submission; the “Mavacamten oHCM Economic Evaluation” Excel workbook; and the “Mavacamten-obstructive HCM-Utilisation and Cost Model” Excel workbook; Table 47, p92, of the resubmission; Excel workbooks “Mavacamten obstructive HCM model resubmission_FINAL” Excel workbook and ‘Attachment 19 - Mavacamten-obstructive HCM-Utilisation and Cost Model-Resubmission’.

HCM = hypertrophic cardiomyopathy; MAVA= mavacamten.

^a Sourced from Table 14.1.12.1 in Attachment 12 – EXPLORER-HCM Tables & Figures

^b The submission proposed flat pricing for mavacamten. The daily dose of mavacamten does not affect the drug price as patients will take one mavacamten capsule per day regardless.

^c Dispensed price using the updated PBS fees and mark-up as in July 2022.

^d 12.87=365.25/28*98.64%. The submission’s economic evaluation assumed that 1.36% of patients did not receive any dose of mavacamten. The November 2022 submission stated that 98.64% of patients in the trial did not miss any doses ; however, the number of pills missed in the remaining 1.36% trial subjects was not reported. This assumption was unchanged for the resubmission.

^e The revised number of scripts and drug cost were calculated by assuming 100% compliance rate. 13.04=365.25/28.

^f 12.73=365.25/28*97.56%. The submission’s financial analysis assumed that 2.44% of patients did not receive any dose of mavacamten. The November 2022 submission stated that 97.56% of patients in the trial did not reach 80% of targeted dose ; however, the number of cumulative doses in the remaining 2.44% trial subjects was not reported. This assumption was unchanged for the resubmission.

^g Proportions of patients alive and on treatment at the start of each year sourced from the economic model.

^h Proportion of patients on treatment at the start of each year. The submission stated that 33.90% of patients did not achieve a New York Heart Association (NYHA) class improvement at Week 30 in EXPLORER-HCM. It was assumed that these patients would discontinue treatment, and therefore in each year, for new initiating patients, the persistence rate was calculated as 66.1% (100%-33.90%). In Year 2 and beyond, the applied persistence rate was 93.94% (in patients on treatment in the previous treatment year), based on data from the EXPLORER-LTE cohort of the MAVA-LTE study.

ⁱ Financial estimates for resubmission assumed no patients discontinue treatment.

Blue shading represents information previously considered by the PBAC.

6.59 The DPMQ per pack of mavacamten (28 days treatment) was \$█ (based on the SPA proposed). Assuming 100% compliance, 13.04 packs per patient per year would cost

\$| per patient per year. Treatment is expected to be ongoing for the life of the patient. The resubmission proposed an RSA to cap the gross cost to the PBS/RPBS.

Estimated PBS usage & financial implications

- 6.60 This submission was not considered by DUSC. As for the November 2022 submission, the resubmission applied an epidemiological approach to estimate the prevalent patients treated with mavacamten.
- 6.61 Prior to the November 2022 PBAC meeting, the DUSC stated that the November 2022 submission had underestimated the costs to Government (para. 6.68, mavacamten, Public Summary Document, November 2022 PBAC meeting). The DUSC advised that the financial model could be simplified to use a prevalent pool with uptake assumptions which would reduce double counting and incorrect assumptions. The 2022 pre-PBAC response included changes in response to the DUSC advice, including: removal of a persistent population, removal of a diagnosis rate to determine eligible patients, exclusion of patients well controlled on BB/CCBs that would be ineligible for mavacamten, and an increase in the proportion of patients with obstructive HCM from 37.70% (based on Canepa et al. 2020) to 60.94% (based on Maron et al. 2006) (para. 6.69, mavacamten, Public Summary Document, November 2022 PBAC meeting).
- 6.62 The resubmission estimated that the net cost to the PBS/RPBS was \$70 million to < \$80 million in Year 1 increasing to \$70 million to < \$80 million in Year 6, for a total of \$400 million to < \$500 million over 6 years). This is lower than the costs in the November 2022 pre-PBAC response of \$600 million to < \$700 million over 6 years. The ESC noted that fewer patients were estimated to be treated with mavacamten in the resubmission compared with the 2022 pre-PBAC response. As a workbook was not provided with the 2022 pre-PBAC response this discrepancy could not be verified.
- 6.63 The submission stated that the financial estimates in the resubmission do not include patients expected to access treatment under the grandfather restriction as the PAP currently has no patients enrolled.
- 6.64 A summary of the data sources used and assumptions made to estimate the usage and cost of the requested PBS listing of mavacamten, and the changes relative to the November 2022 submission are provided in Table 18.

Table 18: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Prevalent HCM population	1 in 350 persons Increasing from 60,236 in Year 1 to 64,898 in Year 6	Midpoint of 1 case per 200-500 persons based on Maron et.al, 1995 and Semsarian et.al. 2015 was applied to ABS population > 18 years	Unchanged from the November 2022 submission.
Proportion of patients with obstructive HCM	60.94%	Base case: 60.94% (Maron et al. 2006) November 2022: 37.70%, (Canepa et.al. 2020)	The resubmission's base case using Maron et al. 2006 was consistent with the pre-PBAC response to DUSC (para. 6.69, mavacamten, Public Summary

Public Summary Document – July 2023 PBAC Meeting

Data	Value	Source	Comment
			Document, November 2022 PBAC meeting).
Proportion of obstructive HCM who are NYHA Class II or III	49.54%	Canepa et.al. 2020	Unchanged from the November 2022 submission.
Proportion of obstructive HCM patients with LVEF ≥ 55	88.92%	Canepa et.al. 2020	Unchanged from the November 2022 submission.
Proportion of patients not well controlled on BB/CCB	44.29%	Advisory Board August 2021. Sensitivity analysis: <ul style="list-style-type: none"> 34.29% 54.29% Adler et al., 2017; Sherrid et al., 2013, Spoladore et al., 2020.	Assumption was included in the November 2022 pre-PBAC response (para. 6.69, mavacamten, Public Summary Document, November 2022 PBAC meeting).
Proportion electing treatment (uptake rate)	Yr 1: 61.11% Yr 2: 66.11% Yr 3+: 71.11%	Assumption based on a sponsor advisory board (nine cardiologists).	The assumption is uncertain with respect to likely uptake and therefore the impact on the resulting estimates of use.
Treatment utilisation			
Compliance	97.56%	EXPLORER-HCM The three patients (out of 123) in the mavacamten arm with an overall compliance <80% were considered as 'not compliant'.	Not reasonable, as it assumes 2.44% of patients did not receive any mavacamten dose.
Utilisation across mavacamten strengths (2.5 mg, 5 mg, 10 mg, and 15 mg)	5%:50%:34%:11%	EXPLORER-HCM: Dose levels assumed as per Week 26 dosing, acknowledging anticipated ongoing therapy. Missing and 0 mg doses excluded.	Given the proposed flat pricing, the change in the distribution of strengths has no effect on the results.
Costs			
Mavacamten (28 capsules per pack)	\$2,321.98	Requested published DPMQ (AEMP: \$2,160.70)	A flat price is proposed for all strengths (2.5 mg, 5 mg, 10 mg, and 15 mg) of mavacamten.
	\$█	Requested effective DPMQ (AEMP: \$█) Price reduced from Nov 22 submission (AEMP \$█)	
Patient copayment	PBS: \$10.76 RPBS: \$3.91	PBS statistics for items 11122J, 11123K and 11131W in 2021 (January to December)	Utilisation data from PBS was reasonable.
Public/Private split	Sacubitril/valsartan 97.46%:2.54% PBS:RPBS		
MBS costs			
Transthoracic echocardiogram (TTE)	\$240.05	Fee for MBS items 55126 and 55134	A total of 6 TTE in Year 1 and 4.5 each year thereafter (12 weekly) was reasonable.

Source: Tables 116-124, p231-7 of the November 2022 submission; Table 66 p113 of the resubmission.

ABS = Australian Bureau of Statistics; AEMP = approved ex-manufacturer price; BB = beta-blocker; CCB = calcium channel blockers; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub Committee; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; MBS = Medicare Benefits Schedule; NYHA = New York Heart Association; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; TTE = transthoracic echocardiogram.

Blue shading represents information previously considered by the PBAC.

6.65 The estimated use and financial impacts of listing mavacamten are provided in Table 19.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated						
PSCR (resubmission)	1	1	1	1	1	1
Resubmission	1	1	1	1	1	1
November 2022 pre-PBAC response	1	2	2	2	2	2
November 2022 submission	1	1	1	1	1	2
Number of packs per year^a						
PSCR (resubmission)	3	4	4	4	4	7
Resubmission	3	3	3	3	3	5
November 2022 Pre-PBAC response	5	5	6	6	6	6
November 2022 submission	2	8	9	7	3	6
Estimated financial implications of mavacamten						
Cost to PBS/RPBS less co-payments						
PSCR (resubmission)	\$10	\$10	\$11	\$11	\$11	\$12
Resubmission	\$13	\$13	\$13	\$13	\$13	\$13
November 2022 Pre-PBAC response	\$14	\$15	\$15	\$15	\$15	\$15
November 2022 submission	\$18	\$17	\$12	\$10	\$16	\$15
Net financial implications						
Net cost to PBS/RPBS						
PSCR (resubmission)	\$10	\$10	\$11	\$11	\$11	\$12
PSCR (resubmission) with removal of price inflation factor for initiation scripts and formula for annual discontinuation applied ^{b,c}	\$10	\$10	\$11	\$11	\$11	\$12
Resubmission	\$13	\$13	\$13	\$13	\$13	\$13
November 2022 Pre-PBAC response	\$14	\$15	\$15	\$15	\$15	\$15
November 2022 submission	\$18	\$17	\$12	\$10	\$16	\$15
Net cost to MBS						
PSCR (resubmission)	\$19	\$19	\$19	\$19	\$19	\$19
Resubmission	\$19	\$19	\$19	\$19	\$19	\$19
November 2022 submission	\$19	\$19	\$19	\$19	\$19	\$19
Net cost to PBS/RPBS/MBS						
PSCR (resubmission)	\$13	\$10	\$10	\$11	\$11	\$11
Resubmission	\$13	\$13	\$13	\$13	\$16	\$16
November 2022 submission	\$18	\$17	\$12	\$10	\$14	\$15

Source: Table 123, p237 and Table 130, p242 of the November 2022 submission, and Excel workbook 'Mavacamten_obstructive HCM_Utilisation and Cost Model'; Table 68, p114, Table 71, p116, and Table 73, p117 of the resubmission and worksheets '3c. Impact - proposed (eff)' and '5. Impact - net' Mavacamten_obstructive HCM_Utilisation and Cost Model-Resubmission; Attachment 16 - Item 5.05 Pre-PBAC response October 2022.

Public Summary Document – July 2023 PBAC Meeting

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Assuming 12.73 packs per year as estimated by the resubmission, based on a compliance rate of 97.56%.

^b Sensitivity analysis conducted during ESC consideration

^c Formula for annual discontinuation applied formula $1 - \text{EXP}(-(-\text{LN}(1 - 0.05)) / (30 * 7 / 365.25)) * 1$.

Blue shading represents information previously considered by the PBAC.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ 50,000 to < 60,000

⁴ 40,000 to < 50,000

⁵ 60,000 to < 70,000

⁶ 70,000 to < 80,000

⁷ 30,000 to < 40,000

⁸ 10,000 to < 20,000

⁹ 20,000 to < 30,000

¹⁰ \$60 million to < \$70 million

¹¹ \$50 million to < \$60 million

¹² \$40 million to < \$50 million

¹³ \$70 million to < \$80 million

¹⁴ \$90 million to < \$100 million

¹⁵ \$100 million to < \$200 million

¹⁶ \$80 million to < \$90 million

¹⁷ \$20 million to < \$30 million

¹⁸ \$10 million to < \$20 million

¹⁹ \$0 to < \$10 million

6.66 The total cost to the PBS/RPBS was estimated in the resubmission to be \$400 million to < \$500 million over a 6-year period. Adding the impact to the MBS (\$20 million to < \$30 million), the overall net costs to Government health budgets was calculated as \$400 million to < \$500 million. The sensitivity analyses presented in the resubmission focused on the key variables which were added or modified in response to previous comments from DUSC and those presented in the November 2022 submission. The results of the sensitivity analyses show that the key inputs which affect the financial implications by more than 20% over six years are the prevalence of HCM, the proportion of HCM patients with obstructive disease, the proportion of patients not well controlled on BB/CCB, and the proportion of patients who are NYHA class II/III. The financial estimates also assume no patients discontinue treatment, which will overestimate the financial costs to Government. This is an unreasonable assumption. Data from MAVA-LTE (EXPLORER-LTE cohort) indicated that 18.2% of patients discontinued treatment in the pre-pandemic period.

6.67 The PSCR presented a revised set of financial estimates that aligned treatment discontinuation rates with those included in the economic model: a 5% discontinuation rate applied at 30 weeks (denoting the end of the EXPLORER-HCM trial) and then an 8.53% rate annually. However, the PSCR noted that due to the structure of the financial estimates, which do not specifically delineate between pre-30 weeks and post-30 weeks of treatment, necessitates the application of discontinuation at 12 weeks (point of transfer from initial to continuing treatment) and then annually thereafter. To account for this, the price of the initial mavacamten script was artificially increased by a factor of 1.03 (representing the ratio of difference due to the 18 weeks that patients in the financial estimates are not considered on treatment multiplied by the 5% of patients who discontinue). Application of this factor

to increase the price may be inappropriate, given that discontinuations in the economic model appear to be higher than what is applied in the financial estimates. Removing this artificial factor decreased the estimated financial impact reported in the PSCR (Table 19).

- 6.68 Overall the net cost to government was estimated in the PSCR to be \$70 million to < \$80 million in Year 1, decreasing to \$50 million to < \$60 million in Year 6 (total over first six years: \$300 million to < \$400 million (Table 19).
- 6.69 The ESC considered that there remained significant uncertainty in the financials estimates provided in the resubmission and PSCR. These include:
- the prevalence of obstructive HCM in the Australian PBS population with a resting or provokable LVOT gradient \geq 50mm Hg;
 - the proportion of the patient population who are NYHA Class II or III; and
 - the uptake rate of mavacamten.

Table 20: The results of the sensitivity analyses (using the proposed effective price of mavacamten)

Variable	Parameters used in sensitivity analysis	Overall net cost to PBS/RPBS over 6 years	% change over 6 years	
Base case (resubmission)		\$ ¹	-	
SA1	Prevalence of HCM (base case: 1 in 350 persons)	1 in 500 persons	\$ ²	-30%
		1 in 200 persons	\$ ³	75%
SA2	Proportion of HCM patients with obstructive disease (base case: 60.94%)	37.70%	\$ ⁴	-38%
SA3	Proportion of obstructive HCM patients who are NYHA Class II/III (base case: 49.54%)	39.54%	\$ ²	-20%
		64.10%	\$ ⁵	29%
SA4	Proportion of HCM patients not well controlled on BB/CCB (base case: 44.29%)	34.29%	\$ ²	-23%
		54.29%	\$ ⁵	23%
SA5	Mavacamten uptake (base case: 71.11%)	61.11%	\$ ²	-16%
		81.11%	\$ ⁵	16%
SA6	Proportion of obstructive HCM patients with LVEF \geq 55 (base case: 88.92%)	78.92%	\$ ²	-11%
		98.92%	\$ ¹	11%

Source: Compiled during evaluation based on Table79, p122, Table 80, p2123 of the submission and worksheets '2b. Patients – prevalent', '8. ABS population' and 'Prevalent' in Excel workbook Mavacamten_obstructive HCM_ Utilisation and Cost Model-Resubmission.

BBs= beta-blockers; CCBs= calcium channel blockers; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SA = sensitivity analysis.

The redacted values correspond to the following ranges:

¹ \$400 million to < \$500 million

² \$300 million to < \$400 million

³ \$700 million to < \$800 million

⁴ \$200 million to < \$300 million

⁵ \$500 million to < \$600 million

Quality Use of Medicines

6.70 This section was unchanged from the November 2022 submission. Mavacamten was approved for registration by the TGA on 19 September 2022.

6.71 From the November 2022 PSD, the submission outlined a number of educational activities for both health care professionals (HCP) and patients to promote the safe and effective use of medicines in the treatment of obstructive HCM patients with

mavacamten. As addressed in the TGA Delegate’s overview, in the United States mavacamten is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risk of heart failure due to systolic dysfunction. However, no risk minimisation activities, similar to the REMS program in US, were proposed in Australia. The submission did not propose any post-market surveillance study as part of QUM activities.

The DUSC previously considered that there are several risk minimisation strategies that have been employed in the United States of America (USA) to inform health practitioners and consumers of the risks involved with mavacamten. The DUSC noted similar strategies or training programs should also be considered for Australia.

- 6.72 The ESC noted the increased risk of heart failure due to systolic dysfunction associated with mavacamten and the complex and demanding titration schedule with multiple echocardiograms that is required to manage the risk of reduced LVEF. The ESC noted that the number of repeated echocardiograms required may lead to an equity issue in some districts across Australia, where a number of patients may have difficulty accessing the required number of echocardiograms per year. The number of echocardiograms required would also be an increase in patient burden. The ESC also noted that there is a wide variation in the cost to patients of echocardiograms throughout Australia and that this may also lead to equity issues especially in rural and regional Australia where there are fewer cardiologists.

Financial Management – Risk Sharing Arrangements

- 6.73 The PBAC previously considered that an RSA would be required to manage the remaining uncertainties related to the financial impact of mavacamten on the PBS/RPBS. The key issues pertaining to uncertainty in the financial estimates included (para. 7.10, mavacamten, Public Summary Document, November 2022 PBAC meeting; p110 of the resubmission):
- The possibility for mavacamten monotherapy to replace SOC treatment, rather than being used as an add-on therapy due to poor tolerability of BB or CCB or patient preference.
 - A high risk of use outside the restriction in patients with less severe disease, due to peak LVOT gradient being a highly variable measurement in clinical practice.
 - The ESC also noted that a number of patients, particularly older patients with asymmetric left ventricular hypertrophy (LVH) secondary to hypertension, can have a phenotypic appearance of HCM, including the presence of high LVOT gradient at rest or on provocation. These patients can be very difficult to exclude phenotypically from those with genetic HCM. The ESC therefore considered that this also posed a significant risk of leakage.
- 6.74 The resubmission stated that in order to reflect the shared nature intended by an RSA, it was proposed that any expenditure over and above the subsidisation cap be subject to a 1% rebate to Government. The risks identified above would potentially

lead to use in a patient population not assessed for cost effectiveness and therefore the proposed RSA is asking the Government to take on 1% of that financial risk. The ESC felt that this RSA and proposed rebate was likely inadequate and posed an unreasonable proportion of the financial risk on Government.

- 6.75 The resubmission's values for the proposed cap are presented in Table 21. These financial estimates cover a 5-year time period from 2023 to 2027 (totalling \$300 million to < \$400million over 5 years). The financial impact is forecast to be \$400 million to < \$500 million over 6 years.

Table 21: Proposed risk sharing arrangement subsidisation cap proposed in the resubmission

	2023 Year 1	2024 Year 2	2025 Year 3	2026 Year 4	2027 Year 5
Base case	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹
PSCR (resubmission)	\$ ²	\$ ²	\$ ³	\$ ³	\$ ³
PSCR (resubmission) with removal of price inflation factor for initiation scripts and formula for annual discontinuation applied	\$ ²	\$ ²	\$ ³	\$ ³	\$ ³

Source: Table 81, p125 of the resubmission

PSCR = pre-subcommittee response

The redacted values correspond to the following ranges:

¹ \$70 million to < \$80 million

² \$60 million to < \$70 million

³ \$50 million to < \$60 million

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of mavacamten for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (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).
- 7.2 The primary reason for this outcome was due to the economic evaluation.
- 7.3 The PBAC noted the sponsor hearing and consumer comments highlighting the need for additional treatment options for this condition. The PBAC noted the consumer comments highlighting the clinical and quality of life benefits expected with mavacamten therapy compared with standard of care and noted patients describe symptom relief and being more able to carry out daily activities, work, engage in exercise and leisure activities when taking mavacamten.
- 7.4 The PBAC noted the resubmission proposed a revised restriction including a written authority listing for initial therapy and a telephone/online PBS authority for continuing therapy that included a requirement for clinical monitoring by cardiologists or

consultant physicians with experience in the management of hypertrophic cardiomyopathy. The proposed restriction also removed a criterion allowing the use of mavacamten prior to BB treatment. The PBAC considered these amendments were appropriate and aligned with previous advice. However, the PBAC considered there remained a number of issues relating to the proposed restriction and place in therapy for mavacamten.

- 7.5 The PBAC recalled it had previously advised that the proposed restriction should reflect the peak left ventricular outflow tract (LVOT) gradient from the EXPLORER-HCM trial (≥ 50 mm Hg at rest, after Valsalva manoeuvre or exercise) (paragraphs 7.4 and 7.11 mavacamten, public summary document, November 2022 PBAC meeting). The PBAC agreed with the ESC that the arguments made in the re-submission and PSCR did not adequately support the inclusion of a peak LVOT gradient criterion of ≥ 30 mmHg (at rest, after Valsalva manoeuvre, or exercise) for reasons outlined by the ESC (paragraph 3.4). The PBAC reaffirmed that peak LVOT gradient is a highly variable measure of disease severity and that a gradient lower than the inclusion criteria of the pivotal trial (EXPLORER-HCM) would create the potential for access to patients with less severe disease, in whom effectiveness and safety has not been demonstrated. The PBAC considered that continuing treatment with mavacamten would require demonstration of ongoing clinical response.
- 7.6 The PBAC agreed with the ESC that it would be more appropriate to position mavacamten after a patient remained symptomatic after previously receiving trials of both a CCB and a BB (unless intolerant/contraindicated to one or both) rather than after a trial of either a BB or CCB. The PBAC also advised that the proposed restriction should include a definition of familial HCM (i.e. first degree relatives).
- 7.7 The resubmission was based on the EXPLORER-HCM clinical trial (N=251) comparing mavacamten (+/- BB/CCB) with placebo (+/- BB/CCB) in patients with symptomatic obstructive HCM (New York Heart Association [NYHA] II-III and peak LVOT ≥ 50 mmHg). The PBAC recalled that the pivotal trial was small (N=251) and had a short duration of comparative follow-up (30 weeks). The PBAC recalled it had previously considered that based on the pivotal trial, mavacamten provided only a moderate improvement in symptomatic outcomes, with 63.4% of mavacamten patients failing to meet the primary endpoint; 35% did not improve NYHA class; and 49% remained NYHA II/III (i.e. symptomatic). The PBAC noted that mavacamten provided improvement in all secondary outcomes of the EXPLORER-HCM clinical trial and considered that the reduction in brain natriuretic peptide (BNP) may be indicative of disease modification. The Committee also noted that based on a secondary outcome analysis, improvement in NYHA functional class remained relatively stable over time (up to week 180) for mavacamten patients compared with SOC, however noted this analysis was based on a small number of patients (n=13 at baseline) and therefore considered the results inconclusive. The PBAC also noted the lack of improvement in quality of life measures.
- 7.8 The PBAC noted updated data provided in the resubmission for two supporting trials: MAVA-LTE (N=231) and VALOR-HCM (N=112). For VALOR-HCM, the PBAC noted that

despite 43 patients (76.8%) in the placebo group meeting the primary outcome (either through decision to proceed to SRT or remained guideline eligible for SRT) only 2 patients (3.6%) elected to proceed with SRT (the same number that elected to proceed to SRT in the mavacamten arm). The PBAC considered that this illustrated patients remain resistant to undergo SRT despite eligibility and considered the assumption that mavacamten would reduce the number of patients proceeding with SRT was uncertain. Furthermore, the PBAC reaffirmed that there remained no evidence that hospitalisations or deaths would be reduced with mavacamten and considered that patients with HCM are expected to have normal life expectancy.

- 7.9 The PBAC recalled that it previously considered that the primary adverse event of concern was the risk of reduced left ventricular ejection fraction (LVEF) and the ongoing requirement for monitoring with multiple echocardiograms per year. It was also noted that the long-term consequences of treatment compared with SOC were unknown. The PBAC noted that the clinical claim was revised in the resubmission to inferior comparative safety versus SOC. The PBAC considered that this was appropriate and aligned with the clinical evidence and with previous advice (paragraphs 7.7, mavacamten PBAC PSD, November 2022 PBAC meeting).
- 7.10 The PBAC noted that the resubmission provided an economic model with a re-specified base case that incorporated a reduced time horizon (from 25 years to 20 years), a revised data truncation point for the SOC arm (from 46 weeks to 38 weeks), removal of disopyramide, increased discontinuation rates for mavacamten patients due to SAEs at week 30 (from 1.6% to 5.0%) and annually (from 2.8% to 8.53%), a reduced cost for cardiovascular hospitalisation (from \$27,780 to \$12,486) and mavacamten (from \$| to \$| DPMQ). However, the revised base case did not implement several of the PBAC's recommended changes for a respecified base case (paragraphs 7.8 and 7.9, mavacamten public summary document, November 2022 PBAC meeting). The PBAC acknowledged the ESC's advice that a longer time horizon than 10 years would be appropriate for a treatment such as mavacamten and agreed that the proposed 20 year time horizon could be justified, noting that this increased uncertainty over the extrapolated period. The PBAC also agreed that given the uncertainty associated with the long extrapolation in the economic model beyond the short time frame of the EXPLORER-HCM it was important that overall PBS expenditure was tightly controlled with a risk sharing arrangement (RSA) with a 100% rebate over the caps.
- 7.11 The PBAC considered the revised base case ICER of the resubmission (\$35,000 to < \$45,000 per QALY gained) remained underestimated due to optimistic assumptions associated with data truncation, mortality, hospitalisation and SRT rates. The PBAC acknowledged that the pre-PBAC response accepted a data truncation point of 30 weeks in both arms of the economic model. The PBAC considered a respecified base case should also include more conservative assumptions for mortality, hospitalisation and SRT rates. A respecified base case was estimated during PBAC consideration using parameters the PBAC advised should be applied to the economic

model and increased the ICER to \$135,000 to < \$155,000 (Table 16).

- 7.12 The PBAC considered revisions to the financial estimates provided in the PSCR were appropriate, but the estimates remained high for a drug with moderate clinical benefit. There was also a risk of leakage into a patient population with less severe disease given the LVOT gradient required in the restriction is a variable measure and the possibility for mavacamten monotherapy to replace SOC treatment for many patients, rather than being used as an add-on therapy (see paragraph 7.10 mavacamten, Public Summary Document, November 2022 PBAC meeting). The PBAC noted a price reduction would be required to achieve cost-effectiveness which will reduce the financial estimates. However, the Committee reaffirmed its previous advice that an RSA would be required, as this will manage the risk of leakage. The PBAC agreed with the ESC that the resubmission's proposed RSA (Table 21) was inadequate and posed an unreasonable proportion of the financial risk on Government.
- 7.13 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for mavacamten using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- revision to the restriction as outlined in paragraphs 7.47.5 7.5 above–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.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available. The PBAC considered a standard re-entry resubmission that requested mavacamten be PBS listed at the current proposed price would need to reflect a smaller and higher risk subgroup than the patient population suggested by PBAC for the early re-entry resubmission.

- 7.14 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 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.

9 Sponsor's Comment

Bristol-Myers Squibb Australia welcomes the PBAC's decision to resubmit via an early re-entry pathway and looks forward to continuing to work with the PBAC and the Department of Health to provide access to mavacamten for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (HCM).