

**5.05 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 Category 1 submission requested a Section 85, General Schedule Authority Required listing for mavacamten for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (HCM). The PBAC has not previously considered mavacamten for any indication.
- 1.2 Listing was requested based on a cost-effectiveness analysis versus placebo (Table 1).

Table 1: Key components of the clinical issue as presented by the submission

Component	Description
Population	Patients with confirmed symptomatic obstructive hypertrophic cardiomyopathy (HCM)
Intervention	Mavacamten with or without standard of care (BB or CC) The recommended starting dose of mavacamten is 5 mg orally once daily. May be decreased to 2.5 mg/day (where Valsalva LVOT gradient < 20 mmHg) or increased up to 15 mg/day (where Valsalva LVOT gradient ≥ 30 mmHg, symptoms persist and LVEF ≥ 55%).
Comparator	Standard of care (BB or CCB alone).
Outcomes	Primary outcome: proportion of patients who achieved the prespecified composite function endpoint at week 30, defined as: an improvement of ≥ 1.5 mL/kg/min in peak oxygen consumption (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 or CCB) is superior in terms of efficacy and non-inferior in terms of safety compared to SoC (BB or CCB alone).

Source: Table 1, p16-17 of the submission and Table 10, p38-39 of the submission.

BB = beta-blocker; CCB = calcium channel blocker; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; SOC = standard of care

2 Background

Registration status

- 2.1 Mavacamten was registered on 15 September 2022 for the following indication:

CAMZYOS is indicated for the treatment of adults with symptomatic NYHA class II-III obstructive hypertrophic cardiomyopathy.

- 2.2 The PBAC noted the TGA indication requires the presence of obstruction but does not include a value of the left ventricular outflow tract (LVOT) gradient, nor is there a requirement for prior or concomitant beta-blocker/calcium channel blocker (BB/CCB) or disopyramide therapy.
- 2.3 Mavacamten was approved for registration by the United States Food & Drug Administration (FDA) in April 2022 for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive HCM to improve functional capacity and symptoms.

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

3 Requested listing

- 3.1 The requested listing and suggested changes proposed by the Secretariat and the PBAC are presented below (additions are in italics, deletions in 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®
Restriction Summary [new 1] / Treatment of Concept: [new 2]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) (<i>writing only via post/HPOS upload</i>)					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Condition: Symptomatic obstructive hypertrophic cardiomyopathy					
Indication: Symptomatic obstructive hypertrophic cardiomyopathy					
Treatment Phase: Initial treatment					
Clinical criteria:					
Patient must have confirmed symptomatic obstructive hypertrophic cardiomyopathy defined as: unexplained left ventricular hypertrophy with maximal left ventricular wall thickness of ≥15 mm [or ≥13 mm if familial hypertrophic cardiomyopathy]; peak LVOT gradient at least ≥30 mm Hg at rest, after Valsalva manoeuvre or exercise.					
<i>Patient must have confirmed left ventricular hypertrophy due to hypertrophic cardiomyopathy with maximal left ventricular wall thickness which is either (i) greater than or equal to 15 mm, or (ii) greater than or equal to 13 mm if patient has familial hypertrophic cardiomyopathy</i>					
AND					
Clinical criteria:					
<i>Patient must have confirmed peak left ventricular outflow tract (LVOT) gradient of greater than or equal to 50mm Hg at rest, or after provocation with either (i) Valsalva manoeuvre, or (ii) exercise.</i>					
AND					

Public Summary Document – November 2022 PBAC Meeting

	Clinical criteria:
	Patient must have a documented left ventricular ejection fraction (LVEF) of greater than or equal to 55%.
	AND
	Clinical criteria:
	Patient must have received prior treatment with either a beta-blocker or <i>non-dihydropyridine</i> calcium channel blocker, unless at least one of the following is present in relation to the beta-blocker or calcium channel blocker:
	(i) a contraindication listed in the Product Information to beta-blocker / non-dihydropyridine calcium channel blocker therapy as listed in the Product Information,
	(ii) an existing / expected intolerance to <i>beta-blocker / non-dihydropyridine calcium channel blocker therapy.</i>
	(iii) local treatment guidelines recommend initiation of this drug product prior to a beta-blocker therapy.
	AND
	Clinical criteria:
	Patient must be symptomatic with NYHA classes II or III.
	AND
	Clinical criteria:
	The treatment must not be <i>in combination</i> co-administered with disopyramide.
	AND
	<i>The treatment must be administered in combination with either a beta blocker or a non-dihydropyridine CCB unless intolerant or contra-indicated.</i>
	Treatment criteria:
	Must be treated by a cardiologist;
	OR
	Must be treated by a consultant physician with experience in the management of <i>hypertrophic</i> cardiomyopathy.
	Population criteria:
	Patient must be <i>at least</i> aged 18 years of age or older.
	Administrative Advice:
	<i>Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.</i>

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 (Streamlined) (telephone/online PBS Authorities system) [new code 4]				

	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Condition: Symptomatic obstructive hypertrophic cardiomyopathy
	Indication: Symptomatic obstructive hypertrophic cardiomyopathy
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must not be co-administered <i>in combination</i> with disopyramide.
	AND
	<i>The treatment must be administered in combination with either a beta blocker or a non-dihydropyridine CCB unless intolerant or contra-indicated.</i>
	Treatment criteria:
	Must be treated by a cardiologist;
	OR
	Must be treated by a consultant physician with experience in the management of <i>hypertrophic cardiomyopathy</i> .
	<i>Patient must have a documented left ventricular ejection fraction (LVEF) of greater than or equal to 55%.</i>
	Population criteria:
	Patient must be at least aged 18 years of age or older.
	Administrative Advice: <i>Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.</i>
	Authority approval for sufficient therapy to complete the balance of supply may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

- 3.2 The submission proposed initial and continuing treatment criteria. The submission proposed a special pricing arrangement (SPA) with an effective dispensed price for maximum quantity (DPMQ) of \$| and a published DPMQ of \$2,321.92.
- 3.3 The proposed PBS restriction for mavacamten is broader than the inclusion criteria in the key clinical trial (EXPLORER-HCM). The proposed restriction limits eligibility to patients with a peak LVOT gradient of ≥ 30 mmHg at rest, after Valsalva manoeuvre or exercise, whereas patients in the trial had a peak LVOT of ≥ 50 mmHg at rest, after Valsalva manoeuvre or exercise. The former population includes those with milder disease; the latter may be indicated for a surgical or percutaneous procedure, septal reduction therapy (SRT). It is unclear what proportion of patients in Australia have a peak LVOT gradient of 30–49 mmHg at rest. The Pre-Sub-Committee Response (PSCR) maintained that a peak LVOT gradient ≥ 30 mmHg (rest, after Valsalva manoeuvre or post-exercise) is an appropriate threshold for determining treatment eligibility and

considered this threshold in keeping with international clinical practice guidelines¹ and Australian clinical practice. The PSCR highlighted the variability in peak LVOT gradients observed across the three measurements taken at baseline of the EXPLORER-HCM trial and that a proportion of patients had a peak LVOT gradient < 50 mm Hg (Valsalva manoeuvre) at baseline. The ESC agreed that peak LVOT gradient is a highly variable measure of disease severity and considered that different readings can be obtained from the same patient over a relatively short period of time. Therefore, the ESC considered there was a high risk of use in patients with less severe disease not reflected in the key trial. The pre-PBAC response maintained that the cut-off value of ≥ 30 mm Hg is the most appropriate for determining eligibility on the PBS. The PBAC agreed with the ESC that the restriction should reflect the higher peak LVOT gradient from the EXPLORER-HCM trial i.e. peak LVOT gradient < 50 mm Hg and, due to the high variability associated with the measure, a risk sharing arrangement (RSA) also be considered.

- 3.4 Mavacamten monotherapy may be an option for a proportion of patients (i.e. patients contraindicated or intolerant to beta-blockers (BB) or non-dihydropyridine calcium-channel blockers (CCB)). In the EXPLORER-HCM trial, 3.3% and 12.5% of the patients in the mavacamten arm and placebo arm, respectively, were not on CCB or BB treatment at baseline. However, it is unknown whether or not these patients had previously received BB or CCB but discontinued treatment before the trial. The ESC considered that mavacamten monotherapy may replace SOC treatment for many patients, rather than being used as an add-on therapy in clinical practice, due to poor tolerability of BB or CCB or patient preference.
- 3.5 The submission positioned mavacamten as a second line add on treatment where patients remain symptomatic despite treatment with a CCB or BB. As mavacamten is proposed for those who do not respond to, lose response, or are unable to tolerate BB or CCB treatment, it would be considered a second-line treatment for obstructive HCM. However, the submission also proposed mavacamten use prior to BB treatment where local guidelines recommend its use. There was no evidence available which supported mavacamten as a first-line treatment. In the key trial 75.3% of the patients were receiving BB treatment at baseline. The ESC considered that potentially positioning mavacamten before BB therapy was inappropriate and not justified by the clinical evidence. The pre-PBAC response stated that the sponsor was amendable to removing the proposed statement allowing mavacamten use prior to BB treatment where local guidelines recommend its use, and the PBAC considered removing the statement was appropriate.
- 3.6 The ESC noted that cardiomyopathy refers to a diverse group of diseases with variable clinical and pathological features and prognosis. Ischaemic/nonischaemic

¹ Ommen, S. R., *et al.* "2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines." *Circulation* 2020. 142(25): e558-e631.

cardiomyopathy is very different to HCM and the proposed restriction should be amended to include the word ‘hypertrophic’ to identify the eligible population.

- 3.7 The proposed restriction excludes concomitant treatment with disopyramide. This is consistent with the exclusion criteria of the pivotal clinical trial. The clinical trial also excluded concomitant treatment with ranolazine. It may also be appropriate to exclude patients being treated with ranolazine in the proposed restriction.
- 3.8 The proposed restriction does not include a treatment discontinuation criterion. The ESC considered treatment discontinuation may be appropriate although it would be difficult to devise a meaningful and at least partially objective criterion. As per the pivotal clinical trial, the outcome that was considered as an adequate response was:
- An improvement of ≥ 1.5 mL/kg/min maximal oxygen consumption (pVO₂) 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 pVO₂ with no worsening in NYHA Functional Class (Composite 2).

The ESC advised that the cardiopulmonary exercise tests required to measure pVO₂ are not widely accessible and are very infrequently performed. Use of cardiopulmonary exercise tests to determine ongoing eligibility for treatment would require a separate MSAC submission. The ESC considered criteria based on NYHA or the Kansas City Cardiomyopathy Questionnaire (KCCQ) and potentially LVOT gradient could also be considered.

- 3.9 The pre-PBAC response argued that the continuation or cessation of mavacamten treatment should remain a clinical decision made by the treating clinician. However, the PBAC considered a stopping rule remained an important consideration, especially given that almost half (49%) of patients treated with mavacamten remained symptomatic after 30 weeks of treatment (NYHA II/III) (Table 9).

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

4 Population and disease

- 4.1 HCM is a relatively common (1/300-400) 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 LVEF but impaired relaxation of the LV. HCM is predominantly caused by autosomal dominant pathogenic variants in the cardiac sarcomere, most commonly the beta myosin heavy chain 7 (MYH7) or myosin-binding protein C3 (MYBPC3) genes. Although some patients may have HCM without any identified pathogenic variants, the risk of adverse events (e.g. ventricular arrhythmia, heart failure, atrial fibrillation, mortality) is higher in those with pathogenic variants

compared to those without any identified². Approximately two-thirds of individuals with HCM have LVOT obstruction (at rest or on provocation) and are said to have ‘obstructive HCM’. This gradient can show significant variability. One of the hallmarks of HCM is an excess of actin-myosin cross bridges formed in the sarcomere.

- 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, in particular verapamil, is used. These treatments are non-specific to HCM and are not effective in all patients. If symptoms persist, then disopyramide or septal reduction therapy is considered.
- 4.3 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.

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

5 Comparator

- 5.1 The submission nominated the comparator as current standard of care (SOC), which is BB or non-dihydropyridine CCB. This comparator was consistent with the key EXPLORER-HCM trial. The submission proposed mavacamten as a second-line therapy, as an add-on to first-line therapy.
- 5.2 The ESC noted that, although disopyramide may be effective for some patients, there was limited clinical efficacy data available for it, it is often poorly tolerated, and has not been approved for this indication in Australia. It was also noted that surgical or percutaneous septal reduction therapy (SRT) is reserved for the most symptomatic patients in clinical practice. The ESC also noted that from the relevant PBS and MBS data presented in the PSCR that there appears to be minimal clinical usage of disopyramide and SRT in this population and it was considered that listing of mavacamten would likely displace disopyramide and SRT to third-line treatment options. The ESC therefore agreed with the submission that SOC was the appropriate comparator to inform comparative clinical and cost effectiveness.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

² Ommen, S. R., *et al.* "2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines." *Circulation* 2020. 142(25): e558-e631.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (HCPs) (3), an individual and a consumer organisation (Hearts4heart) via the Consumer Comments facility on the PBS website.
- 6.3 The comments from HCPs noted that there are currently a number of therapeutic options for patients with obstructive HCM, including medical therapy (i.e. BBs, CCBs, and disopyramide) and invasive medical procedures (alcohol septal ablation or surgical myectomy). The HCPs described that despite the availability of these therapies, there remains a clinical need among patients not suitable for procedures and/or non-respondent to current medical therapies. HCPs also noted that access to specialist invasive therapies remains limited across parts of Australia and outcomes from these procedures can be suboptimal. HCPs considered that mavacamten represents an alternative therapy that appears to provide symptom relief and functional class improvement.
- 6.4 One individual, who would like access to mavacamten, noted the limitations of BB therapy and the potential for mavacamten to provide an alternative therapy option. The individual noted that the routine monitoring required of mavacamten treatment was a potential disadvantage, however considered that the clinical benefits associated with mavacamten outweighed the additional time required for monitoring.
- 6.5 The PBAC noted the advice received from hearts4heart. Hearts4hearts considered that mavacamten was associated with significant improvements to quality of life and clinical outcomes for symptomatic patients living with HCM and was associated with minimal side effects. Hearts4heart emphasised that mavacamten had potential to significantly improve the daily lives of patients, noting that patients describe feeling less fatigued and more able to engage in physical exercise when taking mavacamten.

Clinical trials

- 6.6 The submission was primarily based on one head-to-head trial comparing mavacamten (+/- BB/CCB) with placebo (+/- BB/CCB) (n=251) (EXPLORER-HCM). Three additional non-comparative studies provided supporting evidence of longer-term safety/efficacy (PIONEER-HCM, PIONEER-OLE and MAVA-LTE). One additional head-to-head trial was included as supporting evidence of mavacamten versus placebo in a severe symptomatic population, with NYHA class III/IV, who had been referred for SRT (VALOR-HCM). This population was considered to be a more severe disease stage than the target population, as they were already being referred for SRT.
- 6.7 Details of the key trial presented in the submission are provided in Table 2.

Table 2: Key trial 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.	2020
	Olivotto et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial	<i>Lancet.</i> 2020; 396(10253): 759-769.
	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	<i>Lancet.</i> 2021; 397(10293): 2467-2475
	Elliott. The end of the beginning for drug therapy in obstructive hypertrophic cardiomyopathy with EXPLORER-HCM.	<i>Cardiovasc Res.</i> 2020; 116(13): e175-e178.
	Burstein Waldman C, Owens A. A plain language summary of the EXPLORER-HCM study: mavacamten for obstructive hypertrophic cardiomyopathy.	<i>Future Cardiol.</i> 2021;17(7): 1269-1275
	Hedge et al. Effect of Mavacamten on Echocardiographic Features in Symptomatic Patients With Obstructive Hypertrophic Cardiomyopathy.	<i>J Am Coll Cardiol.</i> 2021; 78(25): 2518-2532.
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.	<i>J Med Econ.</i> 2022; 25(1): 51-58.	

Source: Table 16, p47-49 of the submission.

6.8 The key features of the direct randomised trial are summarised in Table 3.

Table 3: 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 effectiveness outcomes ^b Safety (e.g. AEs, SAEs, deaths)	NYHA class

AE = adverse event; DB = double blind; HCM = hypertrophic cardiomyopathy; LVOT = left ventricular outflow tract; MC = multi-centre; NYHA = New York Health Association; R = randomised; SAE = serious adverse event.

^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 post-exercise LVOT peak gradient, pVO₂, the proportion of patients who achieve a reduction ≥1 NYHA class and patient-reported outcomes as per the Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score (KCCQ-23 CSS) and (Hypertrophic Cardiomyopathy Symptom Questionnaire, shortness of breath) HCMSQ SoB questionnaires.

6.9 The ESC highlighted one potential concern regarding bias in the EXPLORER-HCM study due to SOC treatment imbalances at baseline between study arms. As shown in Table 4, there was an imbalance in CCB treatment in the trial with more patients in the mavacamten arm on CCB treatment compared to the placebo arm. The placebo arm also had more patients who were not receiving either BB or CCB treatment at baseline compared to the mavacamten arm, meaning that 12.5% of patients in the placebo ± BB/CCB arm were effectively untreated. As a consequence, the benefit observed from mavacamten in the primary composite endpoint and other secondary outcomes may be, at least in part, driven by greater concomitant use of SOC treatment in the mavacamten trial arm (97%), compared to the placebo arm (87.5%). The PBAC agreed

with the ESC but considered the imbalance in baseline CCB treatment was small and not likely to be a key driver of the results.

Table 4: BB/CCB treatment at baseline in the EXPLORER-HCM trial

	Mavacamten arm N=123 n (%)	Placebo arm N=128 n (%)
BB	94 (76.4)	95 (74.2)
CCB	25 (20.3)	17 (13.3)
No CCB or BB	4 (3.3)	16 (12.5)

Source: data from text on p136 of the submission and table 67, p139 of the submission.

BB = beta-blocker, CCB = calcium channel blocker.

Comparative effectiveness

- 6.10 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 peak oxygen consumption (pVO₂) and improvement of one or more 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).
- 6.11 The NYHA function classification system is a commonly used system to categorise patients with HCM and/or heart failure. A higher class represents more severe disease and worse symptoms. Class I means no limitation of physical activity, whereas class II and III represent slight and marked limitations of physical activity. Class IV would be assigned to those unable to carry on any physical activity without discomfort.
- 6.12 Over twice as many patients in the mavacamten arm of the EXPLORER-HCM trial met the primary endpoint as in the placebo arm (36.6% vs 17.2%, OR=2.74, 95% CI 1.51, 5.45).

Table 5: Results of composite endpoint at week 30 in EXPLORER-HCM (ITT population)

Outcome	Mavacamten n with event/N (%)	Placebo n with event/N (%)	Odds ratio (95% CI)	Risk difference (95% CI) ^a
Achieved composite functional endpoint ^b , n (%)	45/123 (36.6%)	22/128 (17.2%)	2.74 (1.51, 5.45)^c p = 0.0005	19.4 (8.67, 30.13)
Proportion of patients with ≥3 mL/kg/min in pVO ₂ and improvement ≥1 NYHA class ^d	25/123 (20.3%)	10/128 (7.8%)	3.01 (1.38, 6.57)^e	12.5 (4.02, 21.01)

Source: Table 43, p101 of the submission.

BB = beta blocker; CCB = calcium channel blocker; CI = confidence interval; ITT = intention to treat; n = number of participants with event; N = total participants in group; NYHA = New York Heart Association; OR = odds ratio pVO₂ = peak oxygen consumption

Bold indicates statistically significant results.

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 an Interactive Web/Voice Response System (IXRS)). Odds ratio was estimated using Cochran-Mantel-Haenszel method. Odds ratio >1 indicates better outcome when compared to placebo. P-value and 95% CI were derived using the exact method.

d 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.

e Calculated during the evaluation, using Stata.

6.13 The PSCR provided disaggregated data on the primary composite outcome (Table 6).

Table 6: Disaggregated comparison between mavacamten and placebo groups for the primary composite outcome at Week 30 (ITT population)

Parameters	Mavacamten (n=123), n (%)	Placebo (n=128), n (%)	Risk difference (95% CI) ^a
Response 1 or response 2 (Composite functional endpoint)	45 (36.6)	22 (17.2)	19.4 (8.67, 30.13)
Response 1	41 (33.3)	18 (14.1)	19.3 (8.99, 29.55)
Response 2	29 (23.6)	14 (10.9)	12.6 (3.39, 21.89)
Response 1, not response 2	16 (13.0)	8 (6.3)	6.8 (-0.52, 14.03)
Response 2, not response 1	4 (3.3)	4 (3.1)	0.1 (-4.22, 4.48)
Response 1 and 2	25 (20.3)	10 (7.8)	12.5 (4.02, 21.02)
Improvement of ≥1 NYHA functional class	80 (65.0)	40 (31.3)	33.7 (NR) ^b
Improvement of ≥1.5 mL/kg/min in pVO ₂	51 (42.5)	32 (25.6)	16.9 (NR) ^b
Improvement of ≥3.0 mL/kg/min in pVO ₂	29 (24.2)	16 (12.8)	11.4 (NR) ^b

Source: EXPLORER-HCM CSR Table 14.2.1.1, PSCR (p6)

CI, confidence interval; ITT=, intention-to-treat; NYHA, New York Heart Association; pVO₂, peak oxygen consumption

Note: Response 1 defined as an improvement in pVO₂ ≥ 1.5 mL/kg/min and NYHA class improved ≥ 1. Response 2 defined as an improvement in pVO₂ ≥ 3.0 mL/kg/min and no worsening in NYHA class.

a While not labelled in the PSCR, figures are assumed to be risk difference.

b calculated in a post-hoc analysis.

6.14 The ESC and PBAC noted that 63.4% of mavacamten patients failed to meet the primary composite endpoint and 35% did not improve in NYHA class. The ESC

considered these results important, noting there is no stopping rule in the proposed PBS restriction and that therapy is considered indefinite.

- 6.15 The PBAC has not previously considered pVO₂ as a surrogate outcome for quality of life (QoL) measures and survival. The submission did not systematically justify pVO₂ as a surrogate outcome as per Appendix 5 of the PBAC guidelines (version 5.0). Based on the available evidence it is plausible that a link between pVO₂ and survival exists, however the validity of the estimated clinically important difference and the nature of the comparative treatment effect relationship remains unclear. However, the ESC was 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.
- 6.16 Mavacamten is proposed for long-term use while the duration of mavacamten therapy in EXPLORER-HCM was only 30 weeks and therefore the long-term comparative effectiveness associated with mavacamten treatment is unknown. The PSCR stated that data from MAVALTE was provided as supportive evidence for long-term effectiveness and safety in the submission. While acknowledging these data were non-comparative, the PSCR and pre-PBAC response stated that it remained supportive of the continued efficacy of mavacamten.
- 6.17 The ESC noted the pre-specified subgroup analyses showed that the primary composite endpoint was met more frequently by patients not treated with a BB compared to those who were treated with a BB, although most patients in the trial were receiving BBs. Conversely, there was no statistically significant difference in treatment effect observed between concomitant use with BBs and non-BB use for all secondary endpoints. The PBAC agreed with the ESC and considered the subgroup analysis of the primary composite endpoint was in keeping with the side effect profile of BBs that includes a reduced exercise capacity.
- 6.18 All secondary endpoints, including the change in post-exercise LVOT peak gradient, NYHA class and both the Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score (KCCQ-23 CSS) and Hypertrophic Cardiomyopathy Symptom Questionnaire, shortness of breath (HCMSQ SoB) domain score showed a significant benefit with mavacamten over SOC.
- 6.19 Patients in the mavacamten arm had significantly greater reductions from baseline to week 30 on post-exercise LVOT peak gradient (mmHg) than those in the placebo arm (Table 7). The least squares difference in amount of change was 35 mmHg, which is considered clinically meaningful.

Table 7: Post-exercise LVOT peak gradient

Endpoint	Mavacamten (N = 123)	Placebo (N = 128)
Baseline, n	122	127
Mean (SD)	86 (34.3)	84 (35.7)
Week 30, n	118	123
Mean (SD)	38 (32.1)	73 (34.9)
Change from Baseline to Week 30 in Post-exercise LVOT Peak Gradient (mmHg), n	117	122
Mean (SD)	-47 (40.3)	-10 (29.6)
LS Mean Difference Mavacamten vs Placebo (95% CI) ^a	-35 (-43.2, -28.1)	
P-value	< 0.0001	

Source: Table 44, p102 of the submission.

CI = confidence interval, LS = least squares, LVOT = left ventricular outflow tract, SD = standard deviation

^a The mean difference estimate, its 95% CI, and p-values are from the ANCOVA which controls for treatment group (mavacamten vs placebo), baseline value of the corresponding endpoint of interest, and the three stratification factors (beta-blocker use, NYHA class, ergometer type based on IXRS).

6.20 Patients in the mavacamten arm had a mean increase in pVO₂ between baseline and 30 weeks of treatment of 1.4 mL/kg/min (whereas patients in the placebo arm had no change in peak oxygen consumption). Based on the study by Swank et al. (2012), an improvement of 1.5 mL/kg/min in pVO₂ would be a clinically important difference³.

Table 8: Peak oxygen consumption (pVO2)

Endpoint	Mavacamten (N = 123)	Placebo (N = 128)
Baseline, n	123	128
Mean (SD)	18.9 (4.86)	19.9 (4.91)
Week 30, n	120	125
Mean (SD)	20.4 (5.36)	19.9 (5.40)
Change from Baseline to Week 30 in pVO ₂ (mL/kg/min), n	120	125
Mean (SD)	1.4 (3.12)	-0.05 (3.02)
LS Mean Difference, Mavacamten vs Placebo (95% CI)	1.4 (0.59, 2.12)	
P-value ^a	0.0006	

Source: Table 45, p103 of the Submission.

CI = confidence interval, LS = least squares, pVO₂ = peak oxygen consumption, SD = standard deviation

^a The mean difference estimate, its 95% CI, and p-values are from the ANCOVA which controls for treatment group (mavacamten vs placebo), baseline value of the corresponding endpoint of interest, and the three stratification factors (beta-blocker use, NYHA class, ergometer type based on IXRS).

6.21 At baseline, all patients in the EXPLORER-HCM trial 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.

³Swank, A. M., et al. (2012). "Modest increase in peak VO₂ is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training." *Circ Heart Fail* 5(5): 579-585.

Table 9: 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 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.

6.22 The Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score (KCCQ-23 CSS) is a patient-reported questionnaire which assesses the level of symptoms (such as fatigue, dyspnoea and oedema) as well the level of functional limitations (physical, emotional and social), scaled from 0 to 100 (higher scores representing fewer symptoms and better functioning). Changes in KCCQ-23 CSS of more than 5 are considered clinically meaningful⁴. In the mavacamten arm, mean change from baseline to Week 30 was an increase of 13.6 points, whereas in the placebo arm, the mean increase was 4.2 points. The difference between arms was clinically meaningful (9.1, 95% CI: 5.46, 12.66). An additional 20.1% of patients experienced a clinically meaningful difference in the mavacamten arm compared with the placebo arm. Treatment was stopped at week 30, which explains the minimal difference at week 38 (which was measured after an 8 week ‘washout’ period).

Table 10: Patients with ≥ 10-point increase from baseline in KCCQ-23 CCS by visit (ITT)

Study Week	Mavacamten (N = 89) n (%)	Placebo (N = 80) n (%)	Mavacamten vs Placebo difference % (95% CI) ^a
6	38 (42.7)	22 (27.5)	-15.2 (-29.5, -0.9)
12	41 (46.1)	28 (35.0)	-11.1 (-25.8, 3.7)
18	51 (57.3)	31 (38.8)	-18.6 (-33.4, -3.7)
30	48 (53.9)	27 (33.8)	-20.2 (-34.9, -5.5)
38	16 (18.0)	16 (20.0)	-2.0 (-9.8, 13.8)

Source: Table 49, p109 of the submission.

95%CI = 95% confidence interval; ITT = intention to treat; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score; N = number of patients who provided response; n is the number of patients with a baseline score ≤ 100 minus 10 (i.e., the clinically meaningful threshold).

Patients with missing data at the post-baseline visit were considered non-responders for that visit.

^a Calculated during the evaluation

6.23 The Hypertrophic Cardiomyopathy Symptom Questionnaire, shortness of breath (HCMSQ SoB) domain, is a patient reported outcome instrument. The HCMSQ is a

⁴ Spertus, J, Peterson, E, Conard, MW, Heidenreich, PA, Krumholz, HM, Jones, P, McCullough, PA, Pina, I, Tooley, J, Weintraub, WS, Rumsfeld, JS & Cardiovascular Outcomes Research, C 2005, 'Monitoring clinical changes in patients with heart failure: a comparison of methods', *Am Heart J*, vol. 150, no. 4, Oct, pp. 707-715.

measure developed by the sponsor. This questionnaire has not been independently validated. By Week 30, HCMSQ SoB domain scores improved across both arms, with decreases of -2.8 for the mavacamten group compared with -0.9 for the placebo group. Score changes of ≥ 2.5 points were considered clinically meaningful. By Week 30, 50% of patients in the mavacamten arm had achieved a clinically meaningful response, compared with 21.3% in the placebo group. Although there was considerable missing data for the HCMSQ outcome, the analyses show that it was unlikely that the missing data introduced attrition bias.

Table 11: Patients with ≥ 2.5 -point decrease in HCMSQ SoB domain score by visit (ITT)

Study Week	Mavacamten (N = 90) (n) %	Placebo (N = 75) (n) %	Mavacamten vs Placebo difference % (95%CI) ^a
4	31 (34.4)	13 (17.3)	-17.1 (-30.4, -3.8)
6	33 (36.7)	17 (22.7)	-14.0 (-27.9, -0.1)
10	38 (42.2)	18 (24.0)	-18.2 (-32.5, -4.0)
14	42 (46.7)	21 (28.0)	-18.7 (-33.3, -4.1)
18	45 (50.0)	24 (32.0)	-18.0 (-32.9, -3.1)
22	40 (44.4)	19 (25.3)	-19.1 (-33.5, -4.7)
26	42 (46.7)	19 (25.3)	-21.3 (-35.8, -6.9)
30	45 (50.0)	16 (21.3)	-28.7 (-42.3, -14.5)
38	12 (13.3)	9 (12.0)	-1.3 (-11.5, 8.9)

Source: Table 51, p112 of the submission

95%CI = 95% confidence interval; HCMSQ SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire, shortness of breath domain; ITT = intention to treat; N = patients who provided responses; n = patients who met the criteria

^a Calculated during the evaluation

6.24 QoL data were collected in the EXPLORER-HCM trial 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 baseline values for both treatment groups, with no statistically significant differences observed between the mavacamten arm and the placebo arm (Table 12).

Table 12: Median (range) EQ-5D-5L results by visit (ITT)

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

6.25 It was noted in the evaluation that the effect of mavacamten on patient-relevant clinical endpoints, such as hospitalisation and mortality, was not investigated and is

therefore unknown. The PSCR stated that the goal of mavacamten treatment is to reduce disease severity through symptomatic improvement and that mortality in this relatively young patient group is most often not related to HCM⁵ and would require long-term follow-up to capture accurately in a trial setting. For these reasons, the PSCR argued that the outcomes assessed in EXPLORER-HCM represent the most appropriate patient-relevant endpoints for the obstructive HCM population, focusing on measurements of improved functional capacity and symptomatic improvement. The ESC and PBAC considered the lack of long-term comparative data for more objective endpoints remained a clinical issue, although agreed with the PSCR that symptomatic improvement, preferably through reduced disease severity, would be the treatment goal of mavacamten, with cardiovascular hospitalisations and mortality due to HCM being very uncommon.

Comparative harms

- 6.26 Comparative harms were reported from the EXPLORER-HCM trial. By the end of Week 30, 87.8% of patients in the mavacamten arm had experienced at least one treatment-emergent adverse event (TEAE). This was higher than in the placebo arm (78.9%). The most common adverse events (AEs) are presented in Table 14. The rate of TEAEs was stated in the submission to be similar across both treatment arms. The proportion of subjects with TEAEs in the musculoskeletal and connective tissue disorders system organ class was greater in the mavacamten group compared with the placebo group (40 subjects, 32.5% vs 29 subjects, 22.7%). Higher rates of TEAEs were also observed in the mavacamten arm in the nervous system disorder category (46 subjects, 37.4% vs 36 subjects, 28.1%).
- 6.27 The ESC noted that the long term comparative harms associated with mavacamten treatment is unknown. The PSCR stated that data from MAVA-LTE was provided as supportive evidence for long-term effectiveness and safety in the submission. Based on these data, no new safety signals were observed.
- 6.28 The ESC noted the primary adverse event of concern was reduced left ventricular ejection fraction (LVEF). The ESC noted this was infrequently observed and reversible with temporary treatment cessation. However, mavacamten is a negative inotrope and will need monitoring with echocardiography every 3 months after dose stabilisation. This is an important consideration and long-term consequences are unknown. Additionally, the effect on arrhythmia risk is unclear. While there did not seem to be any excess arrhythmia seen in the clinical trial, the long-term consequences are again unclear. The pre-PBAC response stated due to the stringent monitoring schedule proposed for mavacamten it is expected that all safety events

5 Maron, M. S., Hellawell, J. L., Lucove, J. C., Farzaneh-Far, R., & Olivotto, I. (2016). Occurrence of clinically diagnosed hypertrophic cardiomyopathy in the United States. *American Journal of Cardiology*, 117(10), 1651–1654. <https://doi.org/10.1016/j.amjcard.2016.02.044>

will be identified early and reflective of those already identified in EXPLORER-HCM and EXPLORER-LTE.

Table 13: Summary of key adverse events in the trials

	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)	RR (95% CI)
Total number of TEAEs	536	495	
Patients with any by Week 38:			
TEAEs	108 (87.8)	104 (81.3)	1.08 (0.97, 1.20)
Serious TEAEs	14 (11.4)	12 (9.4)	1.21 (0.58, 2.52)
Drug-related TEAEs	19 (15.4)	18 (14.1)	1.10 (0.61, 1.99)
Drug-related Serious TEAEs	0	1 (0.8)	0.35 (0.01, 8.43)
Treatment interruption due to TEAEs	3 (2.4)	6 (4.7)	0.52 (0.13, 2.04)
Treatment discontinuation due to TEAEs	2 (1.6)	0	5.20 (0.25, 107.27)
Study discontinuation due to TEAEs	2 (1.6)	1 (0.8)	2.08 (0.19, 22.66)
TEAEs leading to death	0	1 (0.8)	0.35 (0.01, 8.43)

Source: Table 61, p127 of the submission

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RR = relative risk; TEAE = treatment-emergent adverse event

Table 14: TEAEs reported for ≥5% of patients in either treatment group

SOC and PT	Mavacamten (N = 123)		Placebo (N = 129)	
	Week 30 n (%)	Week 38 n (%)	Week 30 n (%)	Week 38 n (%)
Total number of TEAEs	419	536	425	495
Number of patients with at least one TEAE	108 (87.8)	108 (87.8)	101 (78.9)	104 (81.3)
Cardiac disorders				
Atrial fibrillation	8 (6.5)	10 (8.1)	9 (7.0)	10 (7.8)
Palpitations	7 (5.7)	7 (5.7)	9 (7.0)	10 (7.8)
Angina pectoris	1 (0.8)	3 (2.4)	5 (3.9)	7 (5.5)
Gastrointestinal disorders				
Diarrhoea	4 (3.3)	5 (4.1)	6 (4.7)	7 (5.5)
Gastroesophageal reflux disease	6 (4.9)	7 (5.7)	3 (2.3)	3 (2.3)
General disorders and administration site conditions				
Fatigue	6 (4.9)	7 (5.7)	5 (3.9)	7 (5.5)
Infections and infestations				
Nasopharyngitis	14 (11.4)	15 (12.2)	15 (11.7)	19 (14.8)
Upper respiratory tract infection	10 (8.1)	10 (8.1)	6 (4.7)	6 (4.7)
Musculoskeletal and connective tissue disorders				
Back pain	9 (7.3)	10 (8.1)	7 (5.5)	8 (6.3)
Arthralgia	5 (4.1)	7 (5.7)	1 (0.8)	2 (1.6)
Nervous system disorders				
Dizziness	21 (17.1)	26 (21.1)	15 (11.7)	17 (13.3)
Headache	14 (11.4)	15 (12.2)	10 (7.8)	10 (7.8)
Syncope	4 (3.3)	7 (5.7)	2 (1.6)	2 (1.6)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	8 (6.5)	18 (14.6)	10 (7.8)	13 (10.2)
Cough	8 (6.5)	10 (8.1)	4 (3.1)	4 (3.1)

Source: Table 62, pp127-128 of the submission

N = number of patients in total; n = number of patients experiencing adverse event; TEAE = treatment-emergent adverse event
Adverse events experienced at over double the rate in one arm than the other are **bolded**

Benefits/harms

6.29 A summary of the comparative benefits and harms for mavacamten ± BB/CCB versus placebo ± BB/CCB is presented in Table 15.

Table 15: 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)^a	
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) ^a	87.8	78.9	8.9 (-0.27, 18.07) ^a	
Patients with serious TEAE	14/123	12/128	1.21 (0.58, 2.52) ^a	11.4	9.4	2.00 (-5.53, 9.54) ^a	

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

CI = confidence interval; 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

Bold indicates statistically significant results.

Note: 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.

Note: 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.

^a Calculated during the evaluation

6.30 On the basis of direct evidence presented by the submission, for every 100 patients treated with symptomatic obstructive hypertrophic cardiomyopathy treated with mavacamten \pm BB/CCB in comparison with placebo \pm BB/CCB over a 30 Week period:

- Approximately 19 additional patients will achieve either:
 - 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

- 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).
- Approximately 9 additional patients may experience a treatment-emergent adverse event (not statistically significant).
- Approximately 2 additional patients may experience a treatment-emergent serious adverse event (not statistically significant).

Clinical claim

6.31 The submission described mavacamten ± BB/CCB as superior in terms of effectiveness compared to standard of care alone (BB/CCB). The ESC considered this claim was supported. However, a number of key issues persisted:

- The key trial was small and had a short duration of follow-up. Patients (N=251) received 30 weeks of treatment and were followed up for an additional 8 weeks (8 week wash-out period). There are no long-term comparative effectiveness and safety data
- A slight imbalance in the percentage of patients without concomitant SOC (BB/CCB) in the arms of the key trial (12.5% placebo ± BB/CCB arm; 3.3% mavacamten ± BB/CCB arm)
- The applicability of the population in the key clinical trial (restricted to patients with more severe disease) to the proposed PBS population (which also included less severe disease if an LVOT gradient >30 mmHg is included in the restriction).

6.32 The submission described mavacamten ± BB/CCB as non-inferior in terms of safety compared to standard of care alone (BB/CCB). The ESC considered this claim was inadequately supported. The key issues were:

- A greater proportion of patients in the mavacamten arm (87.8%) experienced at least one TEAE compared with the placebo arm (78.9%)
- There is a small but definite risk of a fall in LVEF (left ventricular dysfunction) developing with mavacamten

- No long-term comparative safety data were available, and the extended safety data were non-comparative
- No survival or hospitalisation data were available
- The risk of heart failure due to systolic dysfunction, which is being managed in the US with mavacamten only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

6.33 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.34 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.35 The submission presented a stepped economic evaluation of mavacamten ± BB/CCB compared with BB/CCB alone for treatment of symptomatic obstructive HCM. The economic evaluation was based on the direct randomised trial (EXPLORER-HCM) with additional modelled data. The economic evaluation was presented as a cost-effectiveness analysis and a cost-utility analysis. In the economic model, it was assumed that all patients in both treatment arms receive either BB or CCB. Thus, the treatments compared in the economic evaluation were effectively mavacamten + BB/CCB versus BB/CCB alone. The key components of the economic evaluation are summarised in Table 16, with major economic issues discussed in the following paragraphs.

Table 16: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Mavacamten + BB/CCB vs. BB/CCB alone
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)
Outcomes	Number of responders, life years gained, quality-adjusted life years gained
Methods used to generate results	Markov state transition model
Health states	Four health states: NYHA class I, NYHA class II, NYHA class III/IV, death
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
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).

Component	Summary
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 US 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 the key trial) 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.</p> <p>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 the EXPLORER-HCM trial, 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 (Knyshev et al., 2013). The ESC considered the data sourced for NYHA transitions probabilities for patients receiving SRT + BB/CCB were unreliable and not representative of Australian patients.</p> <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>
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 the EXPLORER-HCM trial.</p> <p>NYHA class I: 0.909; NYHA class II: 0.827; NYHA class III/IV: 0.730</p>
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>

Source: Table 81, p189 and Sections 3.4 to 3.6, pp191-217 of the submission.

ABS = Australian Bureau of Statistics; AR-DRGs = Australian Refined Diagnosis Related Groups; BB = beta-blocker; CCB = calcium channel blocker; EQ-5D = EuroQol 5-Dimensions; HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association; PI = Product Information; SOC = standard of care; SRT = septal reduction therapy

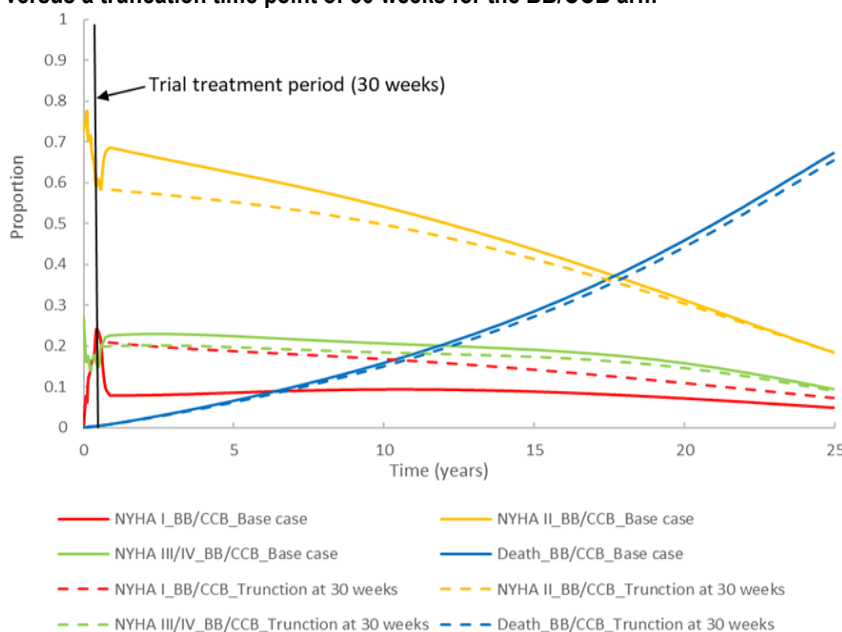
6.36 The economic model assumed a 25-year time horizon. This was selected based on the mean age of the trial population (59 years) and the average life expectancy of the Australian population. This was longer than the time horizon used in the economic

evaluation in the PBAC submissions for tafamidis (for treatment of transthyretin amyloid cardiomyopathy) (20-year time horizon), which represented an older age patient population (mean baseline age in the key trial ATTR-ACT: 74 years vs. 59 years in EXPLORER-HCM). The ESC advised that whilst a 25-year time horizon is appropriate to capture the costs and benefits expected to occur throughout the disease course of symptomatic obstructive HCM, the clinical data from EXPLORER-HCM were inadequate to inform long-term estimates for the nominated time horizon. The ESC therefore suggested that, given the uncertainty in the data, a time horizon of 10 years should also be explored. The ESC noted that almost all incremental life years (LYs) and incremental quality-adjusted life years (QALYs) between the treatment arms accumulated during the extrapolation period.

- 6.37 The economic model assumed an overall survival benefit associated with mavacamten over SOC that was not shown in the clinical data, nor is survival expected to be impacted by mavacamten treatment; as noted in the PSCR, the treatment goal is to reduce disease severity through symptomatic improvement. The PSCR also acknowledged that obstructive HCM is associated with normal life expectancy. The ESC advised that the improvements in functional end points would not necessarily translate into mortality benefits and therefore considered the extrapolated survival gains inappropriate. The pre-PBAC response maintained that the mortality rates associated with the different NYHA classes in the economic model were appropriate.
- 6.38 Results of change in NYHA class applied to the economic model were from a trial with relatively small sample size (N=123–128 in each treatment arm) resulting in a small number of patients in each NYHA class and with a limited follow-up period (38 weeks). 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 US 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 the key trial) to the assumed disease progression rate for BB/CCB. The ESC considered that a constant relative difference over the entire duration of the model was not appropriate. It was also considered that the risk of disease progression would likely increase over time.
- 6.39 Data related to change in NYHA functional class from the EXPLORER-HCM trial was used up to the end of the treatment period, i.e. 30 weeks, for the mavacamten + BB/CCB arm. The submission argued that a potential placebo effect on NYHA class may still be observed for the placebo + BB/CCB group after 30 weeks, and this was supported by the continued worsening of NYHA class (Figure 1). The transition probabilities for BB/CCB monotherapy between Week 30 of the EXPLORER-HCM trial and Week 46, which was the start of the extension study MAVALTE, were also applied to the economic model. The submission assumed that no between-NYHA class transitions occurred after Week 30 for patients receiving mavacamten + BB/CCB and

after Week 48 for patients receiving BB/CCB alone, except for natural disease progression. The purpose of the double-blind, placebo-controlled trial design of EXPLORER-HCM was to account for non-specific effects beyond the action of mavacamten, such as the placebo effect and Hawthorne effect, which existed in both treatment arms, particularly for outcomes such as NYHA classification. Figure 1 shows that the use of a trial data truncation time point at Week 46 for BB/CCB in the base case, instead of at Week 30 (as that for the mavacamten group), results in fewer patients in the comparator arm remaining in the NYHA I class health state (red solid line vs. red dashed line) and more patients in health states that represent more advanced disease. Therefore, the clinical benefit of mavacamten was likely overestimated. The ESC considered the inclusion of the additional 16 weeks of data after the end of the double-blinded treatment period for the comparator arm was not appropriate as this controlled for placebo effect in the comparator arm but not in the mavacamten arm. The ESC noted the model was very sensitive to this input and application of the additional 16 weeks favoured mavacamten. The ESC considered a revised base case should include the same truncation point for both arms of the economic model (30 weeks).

Figure 1: Change in the proportion of patients in each health state in the base case (46 week truncation point) versus a truncation time point of 30 weeks for the BB/CCB arm



Source: Figure constructed during the evaluation, based on the “Mavacamten oHCM Economic Evaluation” Excel workbook. BB = beta-blocker; CCB = calcium channel blocker; NYHA = New York Heart Association

6.40 In EXPLORER-HCM, the proportion of patients who did not receive BB/CCB was 3.3% in the mavacamten arm and 12.5% in the placebo arm; whereas the economic model assumed 100% of patients were treated with a BB/CCB, either in combination with mavacamten or as single-agent therapy for the first 30 weeks. The applicability of the trial results to the economic model were not addressed as no qualitative adjustment to model inputs or sensitivity analysis has been considered.

- 6.41 In the economic model, patients remained on mavacamten + BB/CCB or BB/CCB alone for 30 weeks. Thereafter, patients in the mavacamten + BB/CCB arm were allowed to discontinue treatment due to AEs or lack of efficacy and receive other HCM treatments, including BB/CCB alone, disopyramide + BB/CCB and SRT + BB/CCB. The proportion of patients who discontinued mavacamten due to serious AEs and who experienced no NYHA improvement at Week 30 from baseline was derived from EXPLORER-HCM and applied as a one-off rate to the model at Week 30. Thereafter, a constant per-cycle rate of AE-related treatment discontinuation was assumed. In addition, discontinuation of mavacamten occurred each cycle for patients with worsened NYHA class compared with the prior cycle. The proposed PBS restriction does not include a stopping rule for mavacamten. It is unknown whether the economic model's assumption for mavacamten treatment discontinuation would reflect clinical practice. The ESC did note that 63.4% of mavacamten patients did not achieve the primary composite endpoint and that 48.8% of patients remained NYHA class II/III (see Table 9) and that discontinuation (even without a stopping rule) may be higher than modelled. The ESC considered a revised base case should include stronger justification for long-term treatment discontinuation.
- 6.42 It was assumed that patients treated with BB/CCB alone in the comparator arm or patients who discontinued mavacamten and received BB/CCB monotherapy may subsequently receive additional HCM treatments, i.e. disopyramide or SRT, to BB/CCB monotherapy. The proportion of patients escalating to a subsequent combination and the market share of subsequent treatments were sourced from an Australian advisory board survey. A total of nine Australian cardiologists completed the survey. It was unknown how these clinicians were selected and, thus, whether the opinions from these clinicians would represent Australian clinical practice.
- 6.43 The economic model assumed that patients receiving disopyramide + BB/CCB would experience no improvement in NYHA class from the time of treatment initiation, but have their functional class worsened at the same rate as natural disease progression estimated for the patients receiving only BB/CCB. There are a number of cohort studies⁶ which provide consistent evidence on the treatment benefits of disopyramide, in terms of NYHA class improvement, for treatment of obstructive HCM. As a higher proportion of patients in the BB/CCB alone arm had worsened NYHA class and received disopyramide + BB/CCB, the assumption of nil treatment effect for disopyramide favoured mavacamten. The PSCR disagreed with the evaluation and considered the clinical evidence identified for disopyramide did not conclusively

⁶ Sherrid MV, Shetty A, *et al*, (2013), 'Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with β -blockade or verapamil', *Circulation Heart failure*, 6(4):694-702.
Sherrid MV, Barac I, *et al*, (1005), 'Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy', *Journal of the American College of Cardiology*, 45(8):1251-8.
Haruki S, Minami Y, *et al* (2015), 'Effects of flecainide on left ventricular pressure gradient and symptoms in obstructive hypertrophic cardiomyopathy: a comparison of flecainide and disopyramide', *Heart and vessels*, 30(5):604-10.

demonstrate an improvement in NYHA class. Therefore, the PSCR maintained the addition of disopyramide to BB/CCB as a subsequent treatment option provides no added clinical benefit. The ESC considered including costs of subsequent therapies, but no benefit, was not appropriate and that a more conservative relative treatment benefit should be considered when patients go on to an active subsequent therapy.

- 6.44 In the economic model, patients treated with SRT transitioned to a post-SRT state and were assumed to receive BB/CCB after one cycle. The transition probabilities among NYHA class health states associated with SRT were derived from a small Ukrainian study⁷. The majority of the subjects receiving SRT in this study had NYHA class I or II (33 out of 42, 79%). This is not consistent with clinical practice in Australia where SRT is generally considered for patients for whom maximal tolerated medical therapy is not sufficient to relieve significant symptoms, i.e. NYHA class III/IV. The ESC considered the transition probabilities sourced from this study were not representative of Australian patients and were unreliable, especially as these estimates were based on a total of only nine patients.
- 6.45 The economic model assumed different mortality rates based on patient NYHA class in each model cycle. The mortality rate applied to the NYHA class I patients was estimated based on the all-cause mortality rates in the general population derived from Australian Bureau of Statistics (ABS) Life Tables. For patients with NYHA classes II and III/IV, hazard ratios (HRs) were applied to the ABS mortality data to reflect the increased risk of death in these patients. The mortality HRs assumed in the base case were based on adjusted analyses using the Sarcomeric Human Cardiomyopathy Registry (SHaRe). The approach the submission took to estimate a single HR applied to the NYHA III/IV health state of the economic model appeared unreasonable. The distribution of NYHA III and NYHA IV in the combined NYHA III/IV population is expected to vary over time due to disease progression. The application of a constant HR suggesting a constant weighting of NYHA III/IV hazards was not well justified in the submission.
- 6.46 Table 17 summarises the change in the number of deaths and in the number of SRT procedures received between the two treatment groups over the 25-year time horizon.

⁷ Knyshov G, Lazoryshynets V, *et al*, (2013), 'Is surgery the gold standard in the treatment of obstructive hypertrophic cardiomyopathy?', *Interactive cardiovascular and thoracic surgery*, 16(1):5-9.

Table 17: Average cumulative probability of mortality and SRT per patient over time in the economic model

	Mortality ^a			SRT ^b		
	Mavacamten + BB/CC	BB/CC	Difference	Mavacamten + BB/CC	BB/CC	Difference
Week 30	0.4%	0.5%	-0.1%	0.0%	0.0%	0.0%
Year 1	0.8%	0.9%	-0.1%	7.4%	1.2%	6.2%
Year 5	4.8%	6.5%	-1.7%	15.8%	19.4%	-3.6%
Year 10	12.0%	15.7%	-3.7%	26.5%	42.2%	-15.7%
Year 15	22.7%	28.5%	-5.7%	35.5%	57.6%	-22.1%
Year 20	38.3%	45.8%	-7.5%	42.0%	65.6%	-23.7%
Year 25	59.1%	67.3%	-8.1%	46.1%	69.1%	-23.0%

Source: Table compiled during the evaluation, based on the "Mavacamten oHCM Economic Evaluation" Excel workbook

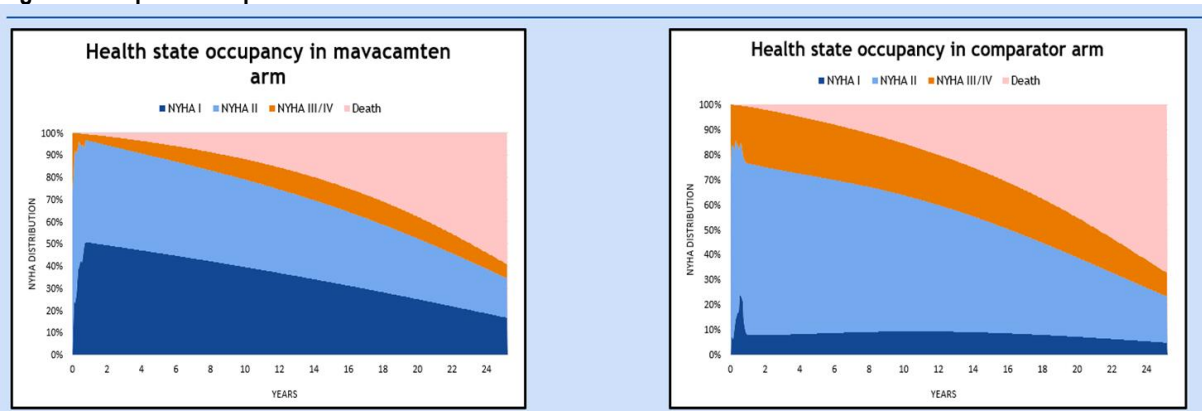
BB = beta-blocker; CCB = calcium-channel blocker; SRT = septal reduction therapy

^a Cumulative deaths were derived from Cells T30:T39 and Cells AZ52:AZ369 in the 'MAVA' and 'Comparator' spreadsheets

^b Proportion of patients receiving SRT was sourced from Cells AR52:AP369 in the 'MAVA' and 'Comparator' spreadsheets

- 6.47 In the economic model, the cumulative percentage of death avoided for mavacamten + BB/CCB versus BB/CCB alone increased over time, from 0.1% at Week 30 to 8.1% at Year 25. The ESC advised it was inappropriate to model mortality gains with mavacamten treatment.
- 6.48 The percentage of patients who received SRT was higher in the mavacamten + BB/CCB arm than in the BB/CCB arm at Year 1 (7.4% vs. 1.2%), due to the application of the one-off treatment discontinuation rate to the mavacamten + BB/CCB arm, but not to the comparator arm, at Week 30. Given the modelled slower natural disease progression associated with mavacamten during the extrapolation period, the cumulative percentage of patients who received SRT became lower in the mavacamten + BB/CCB arm than in the BB/CCB arm from Year 3.7, with the difference reaching a maximum of -23.7% at around Year 20. Thereafter, the difference in cumulative percentage of patients receiving SRT gradually decreased to -23.0% at Year 25 because of the diminishing group of patients remaining on mavacamten therapy in the intervention arm.
- 6.49 Figure 2 provides the distribution of patients in each health state over the model time horizon.

Figure 2: Proportion of patients in each health state over time



Source: Figure 53, p218 of the submission
 NYHA = New York Heart Association

- 6.50 The health state utility values applied to the economic model were based on the EQ-5D data from EXPLORER-HCM, using an Australian value set⁸. Given the short follow-up period of the key trial, the utility decrement associated with deterioration in HCM patients over time was not fully captured in the trial. In addition, patients with NYHA class IV were underrepresented in EXPLORER-HCM, as the clinical study report indicated that none of the trial subjects worsened from NYHA II/III at baseline to NYHA IV at Week 30. Overall, the health state utility values applied to the model may have been overestimated in the economic evaluation, especially the utility associated with the NYHA III/IV health state.
- 6.51 Cost offsets for mavacamten + BB/CCB versus BB/CCB alone were primarily due to the reduced health care resource use associated with disease management in patients of NYHA classes II and III/IV (Table 18). The main cost source of disease management was from cardiovascular hospitalisations. The cost per cardiovascular hospital admission was estimated based on the Australian Refined Diagnosis Related Groups (AR-DRGs) Round 23 (2018-19) National Hospitals Cost Data Collection (NHCDC) Report, using the weighted average of F09A/F09B relating to “Other cardiothoracic interventions without cardiopulmonary bypass pump”. The selection of these AR-DRG codes was not justified in the submission. The average costs per hospital admission for heart failure reported by the Australian Institute of Health and Welfare (AIHW) (2015)⁹ (\$5,600-\$12,900 depending on the presence/absence of complications), after taking into account the inflation factor, are between a quarter and a half of the submission’s estimate (\$27,780). Given that the mean time in NYHA classes II and III/IV was much longer for patients in the comparator BB/CCB arm than for mavacamten patients (Table 18), patients in the comparator arm incurred more hospitalisations due to cardiovascular events. This overestimation of the hospitalisation cost per episode therefore favoured mavacamten. The ESC agreed with the evaluation and considered that the cost assumed for cardiovascular hospitalisation was overestimated. The ESC advised it was inappropriate to equate hospitalisation rates in HFrEF or HFpEF with those in HCM for the same degree of NYHA severity. The ESC considered a revised base case should remove differences in hospitalisations given the lack of clinical trial evidence or clinical experience of hospitalisation due to HCM.

⁸ Viney R, Norman R, *et al*, (2011), ‘Time trade-off derived EQ-5D weights for Australia’, *Value in health*, 14(6):928-36.

⁹Australian 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>

Table 18: Disaggregated summary of cost impacts and health outcome impacts in the economic evaluation (discounted)

Cost (discounted)	Mavacamten + BB/CCB	BB/CCB	Increment	% of total increment
Costs				
Treatments	\$	\$30,481	\$	254.6%
Drug monitoring	\$8,112	\$2,295	\$5,817	13.3%
Disease management				
NYHA class I	\$512	\$116	\$396	0.9%
NYHA class II	\$62,299	\$85,109	-\$22,811	-52.3%
NYHA class III/IV	\$32,766	\$82,779	-\$50,013	-114.7%
Terminal care	\$4,777	\$5,605	-\$828	-1.9%
Total	\$	\$206,385	\$	100.0%
Life years				
NYHA I	5.64	1.28	4.36	807.0%
NYHA II	5.61	7.67	-2.05	-380.3%
NYHA III/IV	1.16	2.92	-1.76	-326.7%
Total LYs	12.41	11.87	0.54	100.0%

Source: Table 110 and Table 111, p223 of the submission.

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

6.52 Subsequent SRT was costed as a weighted separation based on the average of F05A/F05B (“Coronary bypass with invasive cardiac investigation”) for myectomy and F08A/F08B/F08C (“Major reconstructive vascular interventions without cardiopulmonary bypass pump”) for alcohol septal ablation. The usual length of hospital stay reported in the literature¹⁰ was much shorter than – approximately half – the average length of hospital stay associated with the submission’s selected hospitalisation codes (myectomy: 6-9 days vs. 13-19 days; alcohol septal ablation: 3-5 days vs. 5-8 days). It is likely that the cost for SRT has been overestimated in the economic evaluation. This favoured mavacamten, as a higher proportion of patients would escalate to SRT+BB/CCB in the comparator arm than in the mavacamten arm.

6.53 Key drivers of the model are summarised in Table 19.

¹⁰ Yang Q, Zhu C, *et al*, (2021), ‘Surgical septal myectomy outcome for obstructive hypertrophic cardiomyopathy after alcohol septal ablation’, *Journal of Thoracic Disease*, 13(2):1055-65.

Steggerda RC, Damman K, *et al*, (2014), ‘Periprocedural complications and long-term outcome after alcohol septal ablation versus surgical myectomy in hypertrophic obstructive cardiomyopathy: a single-center experience’, *JACC Cardiovascular Interventions*, 7(11):1227-34.

Lemor A, Villablanca PA, *et al*, (2020), ‘Comparison of outcomes of alcohol septal ablation or septal myectomy for hypertrophic cardiomyopathy in patients ≤65 years versus >65 years’, *The American Journal of Cardiology*, 127:128-34.

Table 19: Key drivers of the model

Description	Method/Value	Impact Base case: \$ ¹ /QALY gained
Truncation time point in the BB/CCB arm	46 weeks	High, favoured mavacamten + BB/CCB. Use of trial data up to 30 weeks for the comparator arm increased the ICER to \$ ² /QALY gained.
Efficacy of disopyramide + BB/CCB	Nil treatment benefits. Patients receiving disopyramide would follow natural disease progression of obstructive HCM.	High, favoured mavacamten + BB/CCB. Applying the transition probabilities as observed in the trial for mavacamten + BB/CCB or placebo + BB/CCB increased the ICER to \$ ³ - \$ ⁴ /QALY gained.
Cost of cardiovascular hospitalisation associated with disease management	\$27,800 per hospital admission	High, favoured mavacamten + BB/CCB. Reducing the hospital cost by 2/3 increased the ICER to \$ ² /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 \$ ⁴ /QALY gained.
Efficacy of SRT + BB/CCB	Based on a Ukrainian study by Knyshev et al 2021	Moderate, favoured mavacamten + BB/CCB. Use of sponsor's advisory board inputs increased the ICER to \$ ⁵ /QALY gained.
Utilities	NYHA class I: 0.909 NYHA class II: 0.827 NYHA class III/IV: 0.730	Moderate, favoured BB/CCB alone. Use of lower health state utilities estimated based on the economic model in the tafamidis March 2021 submission reduced the ICER to \$ ¹ /QALY gained.
Time horizon	25 years	Moderate, favoured mavacamten + BB/CCB. Use of a shorter time horizon of 15 years or 20 years increased the ICER to \$ ⁵ /QALY gained or \$ ³ /QALY gained, respectively.
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.	Moderate, favoured mavacamten. All cause/general mortality not NYHA specific (1.0 across all NYHA classes) increase ICER to \$ ⁵ .

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; HCM = hypertrophic cardiomyopathy; ICER = incremental cost-effectiveness ratio; NYHA = New York Heart Association; QALY = quality-adjusted life year; SHaRe = Sarcomeric Human Cardiomyopathy Registry

The redacted values correspond to the following ranges:

- ¹ \$35,000 to < \$45,000
- ² \$75,000 to < \$95,000
- ³ \$45,000 to < \$55,000
- ⁴ \$95,000 to < \$115,000
- ⁵ \$55,000 to < \$75,000

6.54 Results of the economic evaluation are presented in Table 20.

Table 20: Results of the stepped economic evaluation

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

Source: Table 108, p221 of the submission.

BB = beta-blocker; CCB = calcium channel blocker; LYG = life year gained; MAVA = mavacamten; QALYG = quality-adjusted life year gained

^a Proportion of responders, according to the primary composite 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.

The redacted values correspond to the following ranges:

¹ > \$1,055,000

² \$555,000 to < \$655,000

³ \$35,000 to < \$45,000

- 6.55 Results of the stepped economic evaluation indicate that the differences in LYs and QALYs gained between the two treatment arms during the 30-week trial treatment period were minimal (0.0002 LY and 0.02 QALY). The extension of the time horizon from 30 weeks to 25 years greatly increased the incremental health outcomes; and the incremental costs increased beyond 30 weeks as well, but to a lesser extent. The long-term extrapolation period resulted in a more favourable ICER of \$35,000 to < \$45,000/QALY gained, compared with \$555,000 to < \$655,000/QALY gained at Week 30. The model resulted in close to one additional QALY gained, and yet was based on a 38-week trial (with only 30-weeks of active treatment in the mavacamten arm) and which didn't attempt to measure a difference in survival outcomes. The transitions among NYHA health states were sourced from a relatively small number of patients in each health state, especially the higher states. Furthermore, a number of assumptions/inputs used to determine the transition probabilities during the extrapolation period of the economic model were not well justified (refer to Table 16).
- 6.56 The results of key sensitivity analyses presented in the submission and the analyses performed during the evaluation, are summarised in Table 21.

Table 21: Sensitivity analyses

Sensitivity analyses		Incr costs (\$)	Incr QALYs	ICER (\$/QALY)	% change to ICER
Base case			0.98	■ ¹	–
Time horizon (base case: 25 years)					
SA.1	15 years		0.66	■ ²	+26.8%
SA.2	20 years		0.83	■ ³	+10.1%
Discounting rate (base case: 5% for both costs and health outcomes)					
SA.3	0% for both costs and health outcomes ^a		1.74	■ ¹	-21.6%
SA.4	3.5% for both costs and health outcomes ^a		1.14	■ ¹	-7.0%
Trial-based TP truncation time point (base case: 30 weeks for MAVA + BB/CCB and 46 weeks for BB/CCB)					
SA.5	30 weeks for both treatment arms		0.76	■ ⁴	+82.5%
Discontinuation of mavacamten due to lack of response at Week 30 (base case: no improvement in NYHA class)					
SA.6	Worsening in NYHA class		0.97	■ ⁵	+125.1%
SA.7	No discontinuation due to lack of efficacy		0.96	■ ⁵	+131.3%
Efficacy of SRT + BB/CCB (base case: Knyshev et al 2013)					
SA.8	Advisory Board inputs		0.83	■ ²	+43.5%
Efficacy of disopyramide + BB/CCB (base case: nil effects, applying natural disease progression rate as for BB/CCB)					
SA.9	Using last trial-based TP for MAVA + BB/CCB (weeks 26-30), including natural disease progression ^a		0.77	■ ⁴	+73.0%
SA.10	Using trial-based TP for MAVA + BB/CCB at weeks 8-12, including natural disease progression ^a		0.69	■ ⁵	+113.2%
SA.11	Using last trial-based TP for BB/CCB (weeks 38-46), including natural disease progression ^a		0.91	■ ³	+17.9%
SA.12	Using trial-based TP for BB/CCB at weeks 8-12, including natural disease progression ^a		0.82	■ ²	+50.5%
Health state utilities (base case: NYHA I: 0.909, NYHA II: 0.827; NYHA III/IV: 0.730, trial-based)					
SA.13	NYHA I: 0.849; NYHA II: 0.767; NYHA III/IV: 0.50 (based on the economic model presented in the tafamidis March 2021 submission) ^a		1.24	■ ¹	-21.5%
SA.14	Including age-related utility decrement ^a		0.92	■ ³	+6.6%
Cost of hospitalisation associated with SRT (base case: \$55,895)					
SA.15	Reduced by 50% (i.e. \$27,947 per SRT-associated hospital admission) ^a		0.98	■ ³	+11.9%
Cost per hospital admission due to a cardiovascular event (base case: \$27,800)					
SA.16	Reduced by 66.7% (i.e. \$9,267 per hospital admission) ^a		0.98	■ ⁴	+108.2%
Drug costs and MBS costs (base case: PBS mark-up/fees and MBS Schedule fees as in the submission)					
SA.17	Using updated PBS fees/mark-up and MBS fees as in July 2022 and including one-off price increase applied to metoprolol and atenolol in October 2022 ^a		0.98	■ ¹	+0.2%
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)^b					
SA.23	All cause/general mortality not NYHA specific (1.0 across all NYHA classes)		0.58	■ ²	+27.0%
SA.24	1.0 for NYHA I, 1.51 for NYHA II and 2.77 for NYHA III/IV, based on Humedica EMR data		0.93	■ ³	+0.9%
SA.25	1.0 for NYHA I, 2.38 for NYHA II and 9.38 for NYHA III/IV, based on Lakdawala et al (2021) unadjusted		1.61	■ ¹	-15.2%

SA.26	2.0 for NYHA I, 2.96 for NYHA II and 6.34 for NYHA III, doubling the mortality rate in NYHA I patients, with relative mortality HRs for NYHA II and III vs. NYHA I based on the SHaRe adjusted ^a		1.09	■ ¹	-2.8%
Multivariate sensitivity analyses					
SA.5+SA.9			0.62	■ ⁶	+162.2%
SA.5+SA.9+SA.15+SA.16			0.62	■ ⁷	+284.4%
SA.5+SA.9+SA.15+SA.16+SA.13+SA.14			0.76	■ ⁸	+212.3%
SA.5+SA.9+SA.15+SA.16+SA.13+SA.14+SA.6			0.66	■ ⁷	+455.6%
SA.5+SA.9+SA.15+SA.16+SA.13+SA.14+SA.6+SA.8			0.50	■ ⁹	+647.4%

Source: Table 115, pp228-229 of the submission and compiled during the evaluation, based on the 'Mavacamten oHCM Economic Evaluation' Excel workbook

BB = beta-blocker; CCB = calcium channel blocker; ICER = incremental cost-effectiveness; MAVA = mavacamten; QALY = quality-adjusted life year; NYHA = New York Heart Association; SRT = septal reduction therapy; TP = transition probability

a Sensitivity analyses performed during the evaluation.

b Sensitivity analyses performed during ESC evaluation.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$55,000 to < \$75,000

³ \$45,000 to < \$55,000

⁴ \$75,000 to < \$95,000

⁵ \$95,000 to < \$115,000

⁶ \$115,000 to < \$135,000

⁷ \$155,000 to < \$255,000

⁸ \$135,000 to < \$155,000

⁹ \$255,000 to < \$355,000

6.57 Results of key sensitivity analyses indicated that the model was very sensitive to the trial data truncation time point in the BB/CCB alone arm, the efficacy of subsequent disopyramide + BB/CCB therapy, the cost per hospital admission due to a cardiovascular event, and the assumption of mavacamten treatment discontinuation due to lack of efficacy. Variables which moderately affected the ICER included health state utilities, treatment benefits from SRT, time horizon and discounting rate. All sensitivity analyses increased the ICER, except the analysis that assumed lower health state utilities and analyses using discounting rates less than 5%. As shown in the multivariate sensitivity analyses the impact of these model inputs changed markedly where multiple re-specifications were implemented.

6.58 The sensitivity analysis removing the mortality benefit and assuming normal life expectancy increased the ICER to \$55,000 to < \$75,000/QALY gained (SA.23).

Drug cost/patient/year

6.59 A comparison of the drug cost of mavacamten estimated based on the EXPLORER-HCM trial, in the economic evaluation and in the financial analysis is presented in Table 22. 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 22: Drug cost per patient for mavacamten

	Trial dose and duration	Model	Financial estimates
Mean dose	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)
Cost/patient/year	–	\$ ^d (\$ ^e)	\$ ^f (\$ ^e)
Proportion of patients on treatment	At 30 weeks, 3.3% of patients in the mavacamten arm of the EXPLORER-HCM trial 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 submission; the “Mavacamten oHCM Economic Evaluation” Excel workbook; and the “Mavacamten-obstructive HCM-Utilisation and Cost Model” Excel workbook

^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 submission stated that 98.64% of patients in the trial did not miss any doses (p211); however, the number of pills missed in the remaining 1.36% trial subjects was not reported.

^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 submission stated that 97.56% of patients in the trial did not reach 80% of targeted dose (p234); however, the number of cumulative doses in the remaining 2.44% trial subjects was not reported.

^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.

Estimated PBS usage & financial implications

6.60 This submission was considered by DUSC.

6.61 The submission presented an epidemiological approach to estimate the use and financial implications of the proposed listing of mavacamten. The key inputs for the financial estimates and their data sources are summarised in Table 23.

Table 23: 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 applied to ABS population >18 years	No data were identified specifically on the Australian prevalence of HCM.
Diagnosis rate	10.95% (Year 1) increasing by 20% per year	Calculation for 10.95% [= (1/3,195)/(1/350)*100] based on data from Maron et.al, 2016 (1/3,195) divided by the midpoint of HCM prevalence reported above (1/350).	The extent of underdiagnosis of HCM is uncertain. Application of this factor may further reduce the diagnosed population.
Proportion of patients with obstructive HCM	37.70%	Canepa et.al. 2020	These proportions reflect the characteristics of patients diagnosed with HCM in the SHaRE Registry. No data is available on treatment with BB/CCB at/before diagnosis.
Proportion of obstructive HCM who are NYHA Class II or III	49.54%	Canepa et.al. 2020	
Proportion of obstructive HCM patients with LVEF ≥55	88.92%	Canepa et.al. 2020	
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.
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.
Persistence	Yr 1: 66.10% Yr 2 to Yr 6: 93.94%	EXPLORER-HCM EXPLORER-LTE Rader et.al. 2022	It is unknown whether the high persistence rate observed in the clinical trial would reflect clinical practice.
Utilisation across mavacamten strengths (2.5mg, 5mg, 10mg, and 15mg)	5%:50%:34%:11%	EXPLORER-HCM: Dose levels assumed as per Week 26 dosing, acknowledging anticipated ongoing therapy. Missing and 0mg doses excluded.	Given the proposed flat pricing, the change in the distribution of strengths has no effect on the results.

Source: Tables 116-122, p231-6 of the submission

BB = beta-blocker; CCB = calcium channel blockers; DPMQ = dispensed price for maximum quantity; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SRT = septal reduction therapy; TTE = transthoracic echocardiogram.

6.62 The estimated use and financial impacts of listing mavacamten are summarised in Table 24.

Table 24: Estimated use and financial implications using the proposed effective price of mavacamten

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients initiating mavacamten treatment	1	1	1	1	1	1
Total treated patients ^a	1	1	1	1	1	2
Number of packs per patient per year ^b	2	3	4	5	6	7
Estimated financial implications of mavacamten						
Cost to PBS/RPBS less copayments (\$)	8	9	10	11	12	13
Net financial implications						
Net cost to PBS/RPBS (\$)	8	9	10	11	12	13
Net cost to MBS (\$)	14	14	14	14	14	14
Net cost to PBS/RPBS/MBS (\$)	8	9	10	11	15	13

Source: Table 123, p237 and Table 130, p242 of the submission, and Excel workbook 'Mavacamten_obstructive HCM_Utilisation and Cost Model'

Note: drug costs were revised during evaluation using the updated PBS mark-up and MBS fees as of July 2022.

^a Assuming a persistence rate of 66.1% in Year 1, and 93.94% in Year 2 and beyond.

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

The redacted values correspond to the following ranges:

- ¹ 500 to < 5,000
- ² 5,000 to < 10,000
- ³ 10,000 to < 20,000
- ⁴ 20,000 to < 30,000
- ⁵ 30,000 to < 40,000
- ⁶ 50,000 to < 60,000
- ⁷ 70,000 to < 80,000
- ⁸ \$10 million to < \$20 million
- ⁹ \$20 million to < \$30 million
- ¹⁰ \$40 million to < \$50 million
- ¹¹ \$60 million to < \$70 million
- ¹² \$80 million to < \$90 million
- ¹³ \$100 million to < \$200 million
- ¹⁴ \$0 to < \$10 million
- ¹⁵ \$90 million to < \$100 million

- 6.63 The total cost to the PBS/RPBS of listing mavacamten using the effective proposed price was estimated to be \$100 million to < \$200 million in Year 6, and a total of \$300 million to < \$400 million in the first 6 years of listing (minor differences were observed when the PBS mark-up and fees were updated).
- 6.64 The estimates did not include any grandfathered patients and the submission did not anticipate that any patients will require grandfathering, if listed.
- 6.65 The estimated financial impact of listing mavacamten presented in the submission was uncertain and may be an underestimate. The main sources of uncertainty in estimating the number of patients likely to receive mavacamten treatment were related to the prevalence and diagnosis rate of HCM, and the proportion of patients with obstructive disease in Australian population.
- 6.66 In addition, the number of patients who are treated BB or CCB but do not respond, lose response, or are unable to tolerate BB or CCB in the first-line treatment was not discussed in the submission. It is unknown whether patients in Study Canepa 2020 had

previously received BB/CCB or were on BB/CCB when the patient characteristics (e.g. proportion of patients with NYHA class II or III and proportion of patients with LVOT gradient of 30 mmHg) were collected.

6.67 The submission conducted the following sensitivity analyses to address the uncertainties regarding the number of patients eligible for treatment (Table 25).

Table 25: 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 ^a	% change over 6 years
Base Case				
SA.1	Prevalence of HCM	1 in 500 persons	\$ ¹	
		1 in 200 persons	\$ ²	-30%
SA.2	Diagnosis rate of HCM	6.26%	\$ ³	75%
		15.65%	\$ ⁴	-43%
SA.3	Proportion of HCM patients with obstructive disease	31.41%	\$ ⁵	43%
		60.94%	\$ ⁶	-17%
SA.4	Proportion of obstructive HCM patients who are NYHA Class II/III	39.54%	\$ ²	62%
		59.54%	\$ ⁵	-20%
		64.10%	\$ ⁵	20%
SA.5	Mavacamten uptake	61.11%	\$ ⁵	29%
		81.11%	\$ ²	-15%
SA.6	Persistence in Year 1	59.49%	\$ ¹	15%
		72.71%	\$ ¹	-5%
	Persistence in Year 2 and onwards	84.55%	\$ ¹	5%
		100.00%	\$ ¹	-5%

Source: Compiled during evaluation based on Table 132, p244 of the submission worksheets '2b. Patients – prevalent', '8. ABS population', and '11. Persistent population' in Excel workbook 'Mavacamten_obstructive HCM_Utilisation and Cost Model'.

DPMQ = dispensed price for maximum quantity; HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association

^a The figures in *italics* are revised during evaluation using the updated PBS mark-up and MBS fees as of July 2022.

The redacted values correspond to the following ranges:

¹ \$300 million to < \$400 million

² \$200 million to < \$300 million

³ \$600 million to < \$700 million

⁴ \$100 million to < \$200 million

⁵ \$400 million to < \$500 million

⁶ \$500 million to < \$600 million

6.68 The DUSC consideration of mavacamten found the estimates presented in the submission to be underestimated. The main issues were considered to be the following:

- Clinician input suggested the LVOT measure is very dynamic and may vary between readings. The DUSC considered that due to this there is a very high probability of use outside the restriction in patients with less severe disease especially in patients who have difficulty tolerating prior therapies such as BBs or CCBs and may result in a cost to the PBS which is up to 62% greater than estimated.

- It was not clear why a diagnosis rate was applied on top of the proportion of symptomatic patients. The DUSC considered that most, if not all, patients who fulfilled the symptomatic criteria would be diagnosed.
 - A persistence rate was applied to a prevalent population. The DUSC considered that this approach was incorrect as the prevalent population already includes patients who continue treatment.
 - The method to forecast the number of treated patients assumes that people who did not opt for treatment in the first year of eligibility would be equally likely to take up treatment in subsequent years. The DUSC considered this assumption was incorrect.
- 6.69 Overall, the DUSC considered that the method used to develop the financial model could be simplified to use a prevalent pool with uptake assumptions which would reduce double counting and incorrect assumptions. The pre-PBAC response provided updated financial estimates in response to the DUSC advice above. The pre-PBAC response stated that the updated financial estimates included the following changes:
- Removal of a persistent population. The updated financial estimates apply a prevalent population approach only. Patients who choose to not receive mavacamten in the first year of eligibility are not equally likely to receive treatment in subsequent years.
 - Removal of a diagnosis rate to determine eligible patients.
 - The inclusion of a proportion of patients whose HCM is well controlled by BB/CCB and would therefore be ineligible for mavacamten (assumed to be 55.71%).
 - An increase to the proportion of patients who have obstructive HCM from 37.70% (Canepa *et.al.* 2020)¹¹ to 60.94% (Maron *et al.* 2006)¹².
- 6.70 The pre-PBAC response considered the updated financial estimates an upper bound estimate of the potential cost of mavacamten to the Australian government.

¹¹ Canepa M, Fumagalli C, Tini G, Vincent-Tompkins J, Day SM, Ashley EA, *et al.* Temporal Trend of Age at Diagnosis in Hypertrophic Cardiomyopathy: An Analysis of the International Sarcomeric Human Cardiomyopathy Registry. *Circulation Heart failure.* 2020;13(9):e007230.

¹² Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, *et al.* Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation.* 2006;114(21):2232-9.

Table 26: Updated estimated use and financial implications using the proposed effective price of mavacamten

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Submission						
Total treated patients	1	1	1	1	1	2
Total packs per year ^a	2	3	4	5	6	7
PBS/RPBS cost (\$)	8	9	10	11	12	13
Patient copayment (\$)	-14	-14	-14	-14	-14	-14
Net PBS/RPBS cost (\$)	8	9	10	11	12	13
Pre-PBAC response						
Total treated patients	1	2	2	2	2	2
Total packs per year ^a	15	15	7	7	7	7
PBS/RPBS cost (\$)	13	13	13	13	13	13
Patient copayment (\$)	-14	-14	-14	-14	-14	-14
Net PBS/RPBS cost (\$)	16	13	13	13	13	13

Source: Pre-PBAC response (p3)

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

The redacted values correspond to the following ranges:

- ¹ 500 to < 5,000
- ² 5,000 to < 10,000
- ³ 10,000 to < 20,000
- ⁴ 20,000 to < 30,000
- ⁵ 30,000 to < 40,000
- ⁶ 50,000 to < 60,000
- ⁷ 70,000 to < 80,000
- ⁸ \$10 million to < \$20 million
- ⁹ \$20 million to < \$30 million
- ¹⁰ \$40 million to < \$50 million
- ¹¹ \$60 million to < \$70 million
- ¹² \$80 million to < \$90 million
- ¹³ \$100 million to < \$200 million
- ¹⁴ \$0 to < \$10 million
- ¹⁵ 60,000 to < 70,000
- ¹⁶ \$90 million to < \$100 million

Quality Use of Medicines (QUM)

6.71 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.

6.72 The DUSC 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.

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 it is likely that mavacamten ± BB/CCB provided at least a short-term, but moderate clinical benefit over standard of care (BB/CCB), in terms of symptomatic improvement, but the longer-term clinical benefit and safety and the impact on other patient-relevant clinical endpoints such as hospitalisations or mortality is unknown. The PBAC considered that the model relied on highly uncertain and optimistic assumptions regarding the long-term clinical benefit and the ICER presented in the submission was underestimated.
- 7.2 The PBAC noted the consumer comments highlighting an unmet clinical need for effective new therapy options for patients not suitable for invasive medical procedures and/or non-respondent to current medical therapies. The PBAC noted the comments highlighted the significant quality of life benefits expected with mavacamten therapy compared with standard of care and noted patients describe feeling less fatigued and more able to engage in physical exercise when taking mavacamten compared with standard of care. The PBAC noted this aligned with the symptomatic improvement in the key trial.
- 7.3 The submission requested a General Schedule Authority Required (Streamlined) listing for the initial and continuing restrictions of mavacamten. Given that mavacamten has a new mechanism of action (myosin inhibitor) and the restriction includes relatively complex clinical criteria defining symptomatic obstructive hypertrophic cardiomyopathy, the PBAC considered that a written authority listing for initial therapy was appropriate. For continuing therapy, 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.
- 7.4 The PBAC noted that the proposed PBS restriction for mavacamten is broader than the inclusion criteria in the key clinical trial (EXPLORER-HCM) and agreed with the ESC that the restriction should reflect the higher peak LVOT gradient from the EXPLORER-HCM trial (≥ 50 mmHg at rest, after Valsalva manoeuvre or exercise). The PBAC also considered removal of the proposed restriction allowing the use of mavacamten prior to BB treatment (where local guidelines allow it) was appropriate.
- 7.5 The submission nominated the comparator as current standard of care (SOC), which is a BB or non-dihydropyridine CCB. The PBAC noted that this comparator was consistent with the key EXPLORER-HCM trial and agreed with the ESC that disopyramide and SRT were not relevant comparators. The PBAC noted that there was limited clinical efficacy data available for disopyramide in obstructive HCM and also noted that it was not approved for this indication in Australia. The PBAC also considered that in clinical practice, disopyramide is rarely used for patients with obstructive HCM and is often poorly tolerated. Similarly, SRT is rarely used in practice,

even where patients are considered eligible, and is available at specialised centres only. For these reasons, the PBAC considered that current SOC was the appropriate comparator.

- 7.6 The primary clinical evidence supporting the clinical claim was the EXPLORER-HCM clinical trial (N=251) comparing mavacamten (+/- BB/CCB) with placebo (+/- BB/CCB) in patients with symptomatic obstructive HCM (NYHA II-III and LVOT \geq 50mmHg). The PBAC noted the pivotal trial was small (N=251) and had a short duration of comparative follow-up (30 weeks). It therefore considered the long-term comparative effectiveness and safety associated with mavacamten \pm BB/CCB treatment versus standard of care was unknown. The PBAC also noted that the pivotal trial reported on symptomatic/functional endpoints only. The PBAC 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). It was noted the goal of therapy is symptomatic improvement, preferably through reduction in disease severity. The effect mavacamten has on other patient relevant outcomes such as hospitalisation and mortality cannot be practically evaluated in trials in HCM patients because 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, as was noted by the ESC, patients with HCM are expected to have normal life expectancy; mavacamten is therefore not expected to provide mortality benefits.
- 7.7 The PBAC considered the claim of non-inferior safety compared with SOC was not adequately supported by the data and was not reasonable for a treatment used primarily as an add-on to SOC. The PBAC noted that a greater proportion of patients in the mavacamten arm (87.8%) experienced at least one treatment-emergent adverse event (TEAE) compared with the placebo arm (78.9%). The PBAC considered that the primary adverse event of concern was reduced left ventricular ejection fraction (LVEF) and noted that the long-term consequences of treatment compared with SOC are unknown.
- 7.8 The PBAC noted that the economic model relied heavily on assumptions in order to extrapolate the short-term trial data (30 weeks) over the model horizon, which added a high level of uncertainty to the modelled costs and outcomes. The PBAC noted a number of key issues with the economic model that had been raised by the evaluation and the ESC:
- The economic model assumed a time horizon of 25 years. While the length of time horizon chosen was considered appropriate to capture the costs and benefits expected to occur throughout the disease course of obstructive HCM, the clinical data from EXPLORER-HCM were inadequate to inform the modelled long-term estimates.

- Different data truncation points were applied to each arm of the model for data related to change in NYHA functional class. Data up to 30 weeks was applied to the mavacamten + BB/CCB arm and an additional 16 weeks of data, after the end of the double-blinded treatment period, was applied to comparator arm (46 weeks).
- The economic model assumed an overall survival benefit associated with mavacamten treatment over SOC based on a constant relative difference over the entire duration of the model in patient NYHA class that was not justified by the clinical data.
- Patients remained on mavacamten + BB/CCB or BB/CCB alone for 30 weeks. Thereafter, patients were allowed to discontinue treatment due to AEs or lack of efficacy and receive other HCM treatments. The proportion of patients who experienced no NYHA improvement at Week 30 from baseline by NYHA class was applied as a one-off input to the model. However, given 63.4% of mavacamten patients did not achieve the primary composite endpoint and that 48.8% of patients remained NYHA class II/III, discontinuation (even without a stopping rule) may be higher than modelled.
- The clinical benefits associated with subsequent therapies were not included in the economic model. Including costs of subsequent therapies but no benefit was not appropriate and a more conservative relative treatment benefit should be considered when patients go on to an active subsequent therapy.
- The cost assumed for cardiovascular hospitalisation was overestimated. It was inappropriate to equate hospitalisation rates in HFrEF or HFpEF with those in HCM for the same degree of NYHA severity given the lack of clinical trial evidence or clinical experience of hospitalisation due to HCM.
- The cost of subsequent septal reduction therapy (SRT) was based on the cost of coronary bypass with invasive cardiac investigation and major reconstructive vascular interventions without cardiopulmonary bypass. Therefore, it is likely that the cost for SRT was overestimated in the economic evaluation.

7.9 Overall, the PBAC considered the model was not a reliable basis for decision making. The PBAC considered that the ICER of \$35,000 to < \$45,000/QALY gained for the submission's base case was underestimated and highly sensitive to a number of uncertainties in the model. The PBAC considered a respecified base case should include the following:

- a 10 year time horizon
- truncation at 30 weeks in both arms
- no mortality benefit
- amended inputs for:
 - cardiovascular hospitalisation rates and costs
 - SRT costs
 - disopyramide benefits

- discontinuation rates.
- 7.10 The PBAC noted the pre-PBAC response provided revised financial estimates that addressed issues raised in the DUSC advice, which the sponsor considered to be the absolute upper end estimate of the potential cost to government for mavacamten. The PBAC considered the revised estimates were a more realistic estimate of the likely utilisation of mavacamten if PBS/RPBS listed. However, the PBAC considered there remained a number of uncertainties including:
- The possibility for mavacamten monotherapy to replace SOC treatment for many patients, rather than being used as an add-on therapy in clinical practice, 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, not reflected in the key trial, due to peak LVOT gradient being a highly variable measurement in clinical practice.
- For these reasons, the PBAC considered a risk sharing arrangement (RSA) would be required to manage the remaining uncertainties related to the financial impact of listing mavacamten on the PBS/RPBS.
- 7.11 The PBAC considered a resubmission for mavacamten should include the following:
- amendment to the proposed PBS restriction, as outlined in paragraph 7.3;
 - revision to the economic model as outlined in paragraph 7.9; and
 - an RSA proposal to manage residual financial uncertainty.
- 7.12 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.
- 7.13 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 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).