SMC2618

mavacamten hard capsules (Camzyos®)

Bristol Myers Squibb Pharmaceuticals Ltd.

08 March 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

mavacamten (Camzyos®) is accepted for use within NHSScotland.

Indication Under Review: treatment of symptomatic (New York Heart Association, NYHA, class II to III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

In a double-blind, randomised, phase III study, the proportion of patients who achieved the composite primary outcome (that assessed exercise capacity and NYHA class) was significantly greater in the mavacamten group compared with placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Mavacamten is a first in class, selective, allosteric, and reversible cardiac myosin inhibitor that normalises contractility, reduces dynamic left ventricular outflow tract obstruction (LVOTO), and improves cardiac filling pressures in patients with hypertrophic cardiomyopathy (HCM).[1, 2]

The recommended dose of mavacamten ranges from 2.5 mg to 15 mg orally once daily, depending on cytochrome P450 (CYP) 2C19 (CYP2C19) metaboliser phenotype and response to treatment. Before treatment initiation, patients' left ventricular ejection fraction (LVEF) should be assessed by echocardiography; if LVEF is <55%, mavacamten treatment should not be initiated. Refer to the Summary of Product Characteristics.[1]

1.2. Disease background

HCM is a chronic disease of the heart muscle that alters its structure and impairs its function. It has a complex pathophysiology and is characterised by hypercontractility of the cardiac muscle, ventricular hypertrophy, and impaired ventricular relaxation.[2, 3] HCM is the most common genetic disease affecting the heart muscle, and it is known that genetic mutations in cardiac sarcomere (the contractile muscle within the heart), are associated with approximately 40% to 60% of HCM cases.[2] Obstructive HCM (oHCM), which represents approximately 66% of HCM cases,[4] is also characterised by the presence of LVOTO; defined as a peak left ventricular outflow gradient ≥30 mmHg at rest or with provocation. Patients with oHCM experience a progressive decline in their cardiac function and are at greater risk of developing heart failure, arrythmias, and have a greater mortality risk (for example from stroke or sudden cardiac death).[2, 3]

1.3. Company proposed position

As an adjunct to individually optimised standard care, where standard care comprises either non-vasodilating beta-blockers or non-dihydropyridine calcium channel blockers as monotherapy. This is in line with the licensed indication.

1.4. Treatment pathway and relevant comparators

At present, there are no disease-specific therapies for oHCM and pharmacological therapy is administered empirically to improve functional capacity and improve symptoms.[2, 3] First-line pharmacological management of oHCM consists of beta-blockers or non-dihydropyridine calcium channel blockers (verapamil or diltiazem) if still symptomatic or intolerant/contraindicated.[2, 3]

The European Society of Cardiology (ESC) advises that mavacamten should be considered as a second-line therapy when optimal medical therapy (with beta-blockers, non-dihydropyridine calcium channel blockers and/or disopyramide is ineffective or poorly tolerated); they advise that it can be co-administered with beta-blockers or non-dihydropyridine calcium channel blockers but cannot recommend its use with disopyramide.[3] The submitting company did not consider disopyramide to be a relevant comparator because it is associated with poor tolerability and supply problems, and therefore is not widely used in clinical practice. However, whilst SMC clinical experts acknowledged these issues, they did consider disopyramide as a potential treatment option in the second-line setting.

If pharmacological treatment is ineffective, non-pharmacological options for oHCM involve invasive cardiac surgery to relieve the LVOTO by reducing septal hypertrophy. The two approaches (ventricular septal myectomy and alcohol septal ablation) are collectively known as septal reduction therapy (SRT).[2, 3] Whilst SRT can be very effective if performed in specialised treatment centres, it is associated with a range of complications (for example atrioventricular block),[3] and surgical mortality rates of approximately 1% to 5% have been reported.[3, 5-7]

1.5. Category for decision-making process

Eligibility for a PACE meeting

Mavacamten meets SMC orphan equivalent criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support mavacamten for this indication comes from the EXPLORER-HCM study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	EXPLORER-HCM[2, 8]
Study Design	An international, randomised, double-blind, parallel group, phase III study.

Eligible Patients	• Adults (≥18 years old) who weighed > 45 kg.
	• Diagnosis of oHCM that is consistent with current AACF/AHA and ESC guidelines:
	  ○ LVWT ≥ 15 mm or ≥ 13 mm with a family history of HCM ***and***
	  ○ LVOT peak gradient ≥ 50 mmHg at rest, during Valsalva manoeuvre, or after exercise.
	• Documented LVEF ≥ 55%.
	• NYHA class II or III symptoms.
	• Resting oxygen saturation ≥ 90%.
	• No treatment (≤ 14 days prior to screening) or planned treatment with a combination of beta-blockers and verapamil or diltiazem.
	• No treatment (≤ 14 days prior to screening) or planned treatment with disopyramide or ranolazine.
	• Patients had to be able to safely perform upright cardiopulmonary exercise testing.

Treatments and randomisation	At week 0, patients were randomised equally to receive mavacamten 5 mg or matching placebo, orally once daily. At week 6, the mavacamten dose could be down-titrated to 2.5 mg once daily (based on mavacamten plasma concentrations and echocardiography responses on week 4). At weeks 8 and 14, the mavacamten dose could be titrated upwards, downwards, or remain unchanged (based on mavacamten plasma concentrations and echocardiography responses on week 6 and 12). After the second dose adjustment at week 14, no additional up-titrations were permitted. If at any subsequent on-treatment study visit (that is weeks 18, 22 or 26) pharmacokinetic and/or pharmacodynamic criteria were met for a decrease in dose, an unscheduled visit was arranged for 2 weeks later to reduce the mavacamten dose. If the mavacamten dose was decreased at any time during the study, the patient was to continue on the reduced dose through Week 30/end of treatment unless safety or tolerability concerns required further dose reduction or discontinuation of study drug. Background beta-blocker, verapamil, or diltiazem treatment was allowed to continue during the study; however, dual therapy with beta-blockers and verapamil or diltiazem was not permitted. Randomisation was stratified according by NYHA class (II or III), current treatment with a beta-blocker (yes or no), planned ergometer used during the study (treadmill or exercise bicycle), and consent for the CMR sub-study (yes or no).

Primary outcome	This was a composite functional outcome, designed specifically for this study, which was defined as achieving one of the following at week 30: • An improvement of ≥1.5 mL/kg per min increase in pVO_2 (by CPET) with a reduction ≥1 NYHA class ***or*** • An improvement of ≥3.0 mL/kg per min increase in pVO_2 (by CPET) with no worsening of NYHA class.
Secondary outcomes	• Mean change in post-exercise LVOT peak gradient from baseline to Week 30. • Mean change in pVO_2 (by CPET) from baseline to Week 30. • Proportion of patients that improved by ≥1 NYHA Class from Baseline to Week 30. • Mean change in KCCQ-23 clinical summary score (CSS), from baseline to Week 30. • Mean change in HCMSQ shortness of breath (SOB) domain score, from baseline to Week 30.
Statistical analysis	Efficacy analyses were performed in the ITT population, which included all patients who underwent randomisation. A hierarchical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The order of the hierarchical testing was the composite primary outcome, followed by the secondary outcomes in the order above.

AACF = American College of Cardiology Foundation; AHA = American Heart Association; AF = atrial fibrillation; CMR = cardiovascular magnetic resonance imaging; CPET = cardiopulmonary exercise testing; ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; HCMSQ = Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire (23-item version); LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; LVWT = left ventricular wall thickness; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; pVO_2 = peak oxygen consumption.

Compared with placebo, a significantly greater proportion of patients in the mavacamten group achieved the composite primary outcome and its individual components (that is improvement in pVO_2 and improvement in or no worsening of NYHA class). Additionally, 20% of patients in the mavacamten group achieved the more stringent combination of the composite primary outcome (that is patients achieving both improvement of ≥3.0 mL/kg/min increase in pVO_2 and an improvement of ≥1 NYHA class), compared with 8% of patients in the placebo group.[2, 8]

Table 2.2. Results of primary and secondary outcomes from the EXPLORER-HCM study.[2, 8]

	Mavacamten (n=123)	**Placebo (n=128)**	**Difference for Mavacamten versus placebo (95% CI, p-value)**
Composite primary outcome			
Proportion of patients that achieved an improvement of ≥1.5 mL/kg per min increase in pVO_2 (by CPET) with a reduction ≥1 NYHA class or an improvement of ≥3.0 mL/kg per min increase in pVO_2 (by CPET) with no worsening of NYHA class, at week 30	37%	17%	19% (8.7 to 30.1) p=0.0005
Components of composite primary outcome			
Proportion of patients that achieved an improvement of ≥1.5 mL/kg per min increase in pVO_2 (by CPET) with a reduction ≥1 NYHA class at week 30	33%	14%	19% (9.0 to 29.6)[a]
Proportion of patients that achieved an improvement of ≥3.0 mL/kg per min increase in pVO_2 (by CPET) with no worsening of NYHA class at week 30	24%	11%	13% (3.4 to 21.9)[a]

Secondary outcomes:			
Mean change in post-exercise LVOT peak gradient from baseline to Week 30 (mmHg)	-47	-10	-36 (-43.2 to -28.1) p<0.0001
Mean change in pVO_2 (by CPET) from baseline to Week 30 (mL/kg per min)	1.4	-0.1	1.4 (0.6 to 2.1) p=0·0006
Proportion of patients that improved by ≥1 NYHA Class from Baseline to Week 30	65%	31%	34% (22.2 to 45.4) p<0.0001
Mean change in KCCQ-23 clinical summary score (CSS), from baseline to Week 30	13.6	4.2	9.1 (5.5 to 12.7) p<0.0001
Mean change in HCMSQ shortness of breath (SoB) domain score, from baseline to Week 30	-2.8	-0.9	-1.8 (-2.4 to -1.2) p<0.0001

[a] not part of the hierarchical testing strategy. Abbreviations: CI = confidence interval; CPET = cardiopulmonary exercise testing; HCMSQ = Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire (23-item version); LVOT = left ventricular outflow tract; mmHg = millimetre of mercury; NYHA = New York Heart Association; pVO2 = peak oxygen consumption.

Longer-term data is available from the EXPLORER-LTE cohort of MAVA-LTE, an ongoing phase II/III open-label, single-arm long-term (up to 5 years) extension study. The EXPLORER-LTE cohort (n=231) consists of patients who completed the EXPLORER-HCM study. Prior to enrolment, all patients underwent an 8-week post-treatment washout period. All participants received a starting dose of mavacamten 5 mg daily irrespective of the dose they received in the EXPLORER-HCM study. Subsequent dose adjustments were made as per protocol-defined dose reduction rules and scheduled dose adjustments during the study. Results from an interim analysis (data cut-off August 2021), where 15% of patients had reached week 96 of mavacamten treatment, showed that patients receiving mavacamten continued to experience therapeutic benefits that were generally consistent with that in EXPLORER-HCM with regards to LVOT gradients, NYHA class, and other cardiac parameters. However, the effect on pVO_2 was not assessed in this study.[2]

2.2. Evidence to support the positioning proposed by the submitting company

In EXPLORER-HCM, the patients who received mavacamten treatment appeared to show consistent benefit for the composite primary outcome across pre-specified subgroups. Additional analyses were conducted to assess between-group differences by beta-blocker use (yes or no) in changes from baseline in measures of patient symptoms (NYHA class), health status (KCCQ-23 CSS), CPET parameters ($pVO_2$and VE/VCO2 slope), cardiac function and structure (LVOT gradient, LVEF, LAVI, and LVMI), and biomarkers of cardiac stress and injury (NT-proBNP and cTnI). These additional analyses were consistent with the primary outcome subgroup analysis of concomitant beta-blocker use.[2]

2.3. Health-related quality of life (HRQoL) outcomes

HRQoL was assessed using the Kansas City Cardiomyopathy Questionnaire (23-item version) clinical summary score (KCCQ-23 CSS) and the Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath domain (HCMSQ SOB). These were both assessed as secondary

outcomes within the hierarchical statistical testing strategy for EXPLORER-HCM and showed clinically meaningful improvements for mavacamten compared with placebo (see Table 2.2). EQ-5D was assessed as an exploratory outcome.

2.4. Supportive studies

VALOR-HCM is an ongoing multicentre, randomised, double-blind, placebo-controlled phase III study, comparing mavacamten with placebo in patients (n=112) with symptomatic oHCM who were eligible for SRT. The primary outcome was a composite of the decision to proceed with SRT prior to or at week 16, or remaining guideline eligible for SRT at week 16. After 16 weeks, a lower proportion of patients in the mavacamten group, compared with the placebo group, decided to proceed with SRT or remained guideline eligible for SRT: 18% (10/56) versus 77% (43/56); treatment difference 59% (95% CI: 44% to 74%); p<0.0001.[2, 9]

At the 32-week database lock, 108 patients qualified for the 32-week evaluation (56 patients originally randomised to the mavacamten group and 52 originally randomised to the placebo group). After the week 16 assessment, patients in the mavacamten group continued this treatment, and patients in the placebo group switched to mavacamten 5 mg once daily. In the previous placebo group, 3.8% (2/52) of patients in the active-controlled period (week 16 to 32) proceeded to SRT, and 5.8% (3/52) of patients remained SRT eligible. These data are similar to those observed in the mavacamten group in the double-blind period. In the previous mavacamten group in the active-controlled period, 1 additional patient decided to proceed to SRT, 1 additional 1patient became guideline eligible for SRT between 16 and 32 weeks, and 1/8 patients who were guideline eligible for SRT after 16 weeks of mavacamten remained guideline eligible at week 32, which suggests maintenance of treatment effect at week 32. Maintenance of effect after 32 weeks of treatment has also been demonstrated for secondary outcomes.[9]

The sustained effects of mavacamten on the primary and secondary endpoints have now been demonstrated to week 56.[10]

3. Summary of Safety Evidence

Overall, mavacamten appears to be generally well tolerated, with dizziness, dyspnoea, and headache being the most frequently reported adverse events (AEs) from a pooled safety database of 207 patients with oHCM (including EXPLORER-HCM, EXPLORER-LTE, and VALOR-HCM) and at least 1 year exposure to mavacamten.[2]

There is an expected effect on LVEF reduction due to the mode of action of mavacamten. In phase III studies, 5% (9/179) patients in the mavacamten group experienced reversible reductions in LVEF<50% while on treatment, which recovered following interruption of mavacamten.[1] Careful monitoring of patients should be carried out in order to manage the risk of heart failure due to systolic dysfunction (LVEF <50%).[1, 2] No other significant safety concerns regarding cardiovascular effects have been identified from the currently available safety data.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Mavacamten is the first medicine to be licensed specifically for the treatment of oHCM.
- EXPLORER-HCM was a well-conducted, randomised, double-blind, phase III study with stratification, and most baseline characteristics were balanced between the two treatment groups; this makes it likely that there is a low risk of bias.
- In EXPLORER-HCM, compared with placebo, mavacamten treatment resulted in significantly greater proportions of patients achieving the composite primary outcome, which assessed exercise capacity (pVO_2) and symptomatic burden (NYHA class); exercise capacity is a known prognostic factor for mortality in oHCM. Statistically significant improvements associated with mavacamten were also observed for all secondary outcomes including post-exercise LVOT gradient, and the HRQoL outcomes KCCQ-23 and the HCMSQ.[2, 11]
- Relevant to the positioning, which is in line with the licensed indication, all patients in EXPLORER-HCM were NYHA class II (73%) or III (27%), and most were on background therapy at baseline with either a beta-blocker (75%) or non-dihydropyridine calcium channel blocker (17%); these background therapies were allowed to continue during the study.[2, 11]
- Results from the phase III study VALOR-HCM support the role of mavacamten in postponing or preventing the need for patients with oHCM to undergo SRT (see section 2.4).[2, 9]
- EXPLORER-HCM and VALOR-HCM demonstrate that mavacamten treatment results in improvements across the entire population of symptomatic NYHA Class II to III oHCM patients.[2]

4.2. Key uncertainties

- There is some uncertainty in whether disopyramide is a relevant comparator, since clinical experts contacted by SMC suggested this as a potential second-line treatment option (used in addition to beta-blocker or non-dihydropyridine calcium channel blockers); experts also stated that disopyramide would most likely be displaced by mavacamten. However, experts noted that disopyramide can cause significant adverse events and that there are problems with the availability of this medicine in the UK,[11] which makes it uncertain what proportion of these patients receive disopyramide in practice. However, it is likely that patients would prefer disopyramide over SRT due to the associated risks of this cardiac surgery (see section 1.4).
- EXPLORER-HCM and EXPLORER-LTE excluded patients who received disopyramide, which means these patient populations may not be fully representative of patients with oHCM in NHSScotland. However, disopyramide was allowed as a concomitant medicine in the VALOR-HCM study where 20% of patients were on disopyramide monotherapy or in combination;[2, 9] this may be more representative of the proportion of patients eligible for mavacamten within the proposed positioning. Given the findings in this study are consistent with those in EXPLORER-HCM, this provides reassurance.

- There is uncertainty about whether the effect of mavacamten on pVO_2 is maintained beyond week 30 in the EXPLORER-HCM study, since this was not assessed in the EXPLORER-LTE study. Given this is a long-term condition, there is a concern about this.

4.3. Clinical expert input

Clinical experts consulted by SMC considered mavacamten to be a therapeutic advancement and fulfils an unmet need for this patient population; since it can provide symptomatic control as well as improvements in quality of life and proxy markers of disease progression. Additionally, it may avoid or reduce the need for invasive cardiac surgery such as SRT in those who do not respond to current standard of care for oHCM.

4.4. Service implications

Clinical experts consulted by SMC advised that the introduction of mavacamten would likely have a significant service impact. The initiation and ongoing use of mavacamten requires intensive echocardiogram monitoring (as per the SPC), and access to this cardiac diagnostic service may be challenging due to echocardiogram capacity.[12]

The dosing of mavacamten requires CYP2C19 genotyping to determine the appropriate mavacamten dose; however, CYP2C19 genotyping is not yet widely established in NHSScotland. Patients on concomitant treatment with inhibitors and inducers of CYP2C19 and CYP3A4 may require specialist review; see SPC for further details.

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information**.**

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Cardiomyopathy UK, which is a registered charity.

- Cardiomyopathy UK has received 13.4% pharmaceutical company funding in the past two years, including from the submitting company.

- Obstructive hypertrophic cardiomyopathy is a highly impactful condition affecting an individual's physical and mental health. The most impactful physical symptoms of the condition are breathlessness, exhaustion, and the inability to carry out day to day tasks.

- Current medication does not provide symptom relief for all and myectomy and septal ablation are not suitable for all individuals.

- The patient group described how mavacamten is seen by the community as a breakthrough as it presents an opportunity for non-invasive treatment. A treatment that manages the symptoms of obstructive hypertrophic cardiomyopathy, in particular breathlessness and exhaustion, would not only reduce the disease burden on people with the condition but also on those caring for them.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime horizon (up to age of 100 years), mean age of patients in the model is 59 years.
Population	The economic evaluation considers the use of mavacamten for the treatment of adults with symptomatic (NYHA class II to III) obstructive HCM alongside best-supportive care (BSC), which consists of beta-blockers or calcium channel blockers.
Comparators	BSC was considered the only relevant comparator and was represented by the placebo arm of the EXPLORER-HCM study, where BSC consists of beta-blockers or calcium channel blockers. In this case the beta-blocker (BB) was propranolol, and the calcium channel blockers (CCB) were verapamil and diltiazem. The submitting company did not consider disopyramide as a relevant comparator but included it as a subsequent treatment, as well as SRT.
Model description	A Markov model consisting of 5 health states was provided which included four NYHA functional classes and a death state. Patients could move through the model by transitioning to a different NYHA state or remain in their current NYHA state. The death state can be reached at any point. The model used variable cycle lengths. Initially, for the first 30 weeks, the cycle lengths were 2 and 4 weeks. Then after week 30, the cycle length changed to 28 days.
Clinical data	The primary source of data was the EXPLORER-HCM study; a phase III, double-blind, randomised study of mavacamten plus BSC versus placebo plus BSC. In the absence of mortality date from the study, the submitting company used intermediate endpoints such as NYHA classification to infer the effect of mavacamten on mortality, assuming a causal relationship between NYHA class and mortality. The mortality hazard ratios were taken from a study by Wang et al (2023) using the Optum Market Clarity database.[13] Longer-term supporting evidence was also presented from MAVA-LTE, a long-term safety extension study of mavacamten in adults with HCM who have completed MAVERICK-HCM or EXPLORER-HCM but this submission only focussed on the EXPLORER-LTE cohort.
Extrapolation	Short-term transition probabilities: In the base case, the data available up to week 30 for the mavacamten plus BB/CCB arm and week 46 in the BB/CCB monotherapy arm were used to inform the model transition probabilities, because at the time of submission they represented the longest continuous data available for each treatment arm. Long-term progression rate: In the base case, the submitting company assumed that long-term disease progression is not dependent on the treatment received. The model used a progression rate of 4.55% assigned to each NYHA class for all treatments (Maron et al, 2016).[14] Subsequent treatments included disopyramide and SRT. The data informing discontinuation rates for both adverse events and lack of response came from the EXPLORER-HCM study.
Quality of life	Assigned health state utility values were informed via analysis of EQ-5D-5L data collected during the EXPLORER-HCM study, then 'cross-walked' into EQ-5D-3L values. These utility values were then capped and adjusted to population norms. Disutilities were not included in the model as the submitting company believed these were captured in the EQ-5D data.
Costs and resource use	Medicine acquisition costs were included in the analysis with no administration costs assumed. Costs for BB/CCB and subsequent therapies (disopyramide and SRT) were also included. Other costs included were health state resource utilisation costs, adverse event costs, end of life, and monitoring costs. The SPC recommends monitoring for mavacamten + BSC, and these costs were included in the model. Mavacamten also requires additional one-off CYP2C19 genotyping, however this cost was not included in the base case.

PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of mavacamten.

6.2. Results

The base case results showed an incremental cost per quality adjusted life year (QALY) of £10,989 with the PAS applied.

The key driver of cost differences in the comparison of mavacamten versus BSC is the differences in medicine acquisition costs, with additional cost for required drug monitoring, as well as cost-savings associated with health care resource utilisation costs. QALY gains are driven mainly by those accrued in the NYHA I health state, as mavacamten plus BSC demonstrated improvements in transitioning patients to lower NYHA class health states compared to the comparator, where patients are more likely to remain in higher NYHA classes.

6.3. Sensitivity analyses

The submitting company conducted thorough sensitivity analyses, covering probabilistic, deterministic and scenario analysis.

	Parameter	Base case	Scenarios	ICER (£/QALY)
0	Base case			£10,989
1	Time horizon	Lifetime (100 years)	20 years	£12,229
2			30 years	£11,953
3	Comparator arm transition probabilities	Trial-based transition probabilities until week 46; no NYHA class transitions beyond week 46 (unless SRT event experienced or due to disease progression)	Trial-based probabilities until week 30; no NYHA class transitions after week 30 (unless SRT event experienced)	£20,009
4	Mavacamten discontinuation from week 30 onwards due to SAEs (annual %)	2.77% annually after week 30	1.4% annually after week 30	£13,189
5	Mortality	HRs from Market Clarity	HRs from Humedica EMR (Wang et al. 2022)[15]	£10,100
6			Adjusted HRs from SHaRe (Appendix D)	£9,036

	Parameter	Base case	Scenarios	ICER (£/QALY)
7	Utilities	Trial-based utilities from EXPLORER-HCM (capped and adjusted for population norms)	Utilities from Göhler *et al*, 2009.[16]	£10,506
8			Utilities from EXPLORER-HCM	£9,968
10	Genotype testing	CYP2C19 genotype testing is not included in the base case	Laboratory testing	£11,082
11			Point of care testing (Genomadix Cube)	£11,121
12	Natural disease progression	4.55% for all treatments	Lower rate of progression on mavacamten, 4.55% otherwise	£10,725
13			Lower rate of progression on mavacamten, disopyramide and after SRT, 4.55% otherwise	£10,838
14			7.4% per year on ALL TREATMENTS (from Maron et al (2016)[14] for "rest obstruction")*	£8,805
15			3.2% per year on ALL TREATMENTS (from Maron et al 2016[14] for "provocable obstruction")*	£12,599
16	Combination 3+15		Combined scenario: - Short-term transition probabilities up to week 30 for comparator arm - 3.2% long-term progression rate	£21,949

17	Combination 11+3+15+1		Combined scenario: - Including genotype testing (point of care) - Short-term transition probabilities up to week 30 for comparator arm - 3.2% long-term progression rate - 20 year time horizon	£26,217

6.4. Key strengths

- Utilising direct randomised control data from the EXPLORER-HCM in the economic modelling is a key strength because it ensures that analyses are grounded in high quality empirical evidence.
- Using utility values derived directly from EQ-5D data from the EXPLORER-HCM study, then adjusting for population norms, minimises some of the uncertainties and enhances the credibility. The utility values identified in published literature and previous SMC submissions for NYHA class I to III were similar to those from EXPLORER-HCM, suggesting the values have face validity.
- The model structure of a Markov model with NYHA class health states is appropriate to reflect the condition. The monthly cycle length has been justified and is reasonable to capture the changes in health states.

6.5. Key uncertainties

- The submitting company did not include disopyramide as a comparator, but instead modelled it as a subsequent therapy option. SMC clinical experts list disopyramide as a potential comparator in the second-line setting, and a preferred treatment option to SRT. However, the experts also noted that disopyramide is not well tolerated and that there are ongoing supply issues in the UK. The Committee agreed with the company's approach, based on feedback from SMC clinical experts regarding the above, as well as the variability of disopyramide usage in clinical practice and acknowledging the scarcity of available evidence to make an informed comparison.

- The approach to short-term transition probabilities, derived from the EXPLORER-HCM study, introduces uncertainties. The model employed short-term transition probabilities up to week 30 for the intervention arm and week 46 in the control arm. This discrepancy means that any benefits or deteriorations occurring between weeks 30 and 46 in the comparator arm are incorporated into the model, but there are no data to directly inform the effect of mavacamten on NYHA class beyond week 30. Further scenarios were requested by the Assessment Team to adjust the comparator arm to only use transition probabilities up to week 30, to make the methodologies consistent across treatment arms. In this analysis (scenario 3) the ICER does increase, raising concerns the base case approach may introduce bias.
- The long-term disease progression rate used by the submitting company is uncertain as it may misrepresent actual progression rates. The base case assumes a uniform disease progression rate across NYHA class, irrespective of treatment, and relies heavily on a single study by Maron et al (2016).[14] This secondary source, while informative, offers limited insights as it only covers transitions between NYHA class I/II to class III/IV, and not individual transitions between each NYHA class. The application of a uniform 4.55% annual progression rate may be an oversimplification. In scenario analyses the progression rates were adjusted as well as varied between different treatment therapies. However, maintains its uniformity across the NYHA classes (scenario 12-15), reflecting a lack of evidence on whether and how rates should differ with worsening NYHA classes. This uniform approach and the dearth of evidence, adds to the uncertainty and possible oversimplification of disease progression in the model.
- The model relies on the assumption that there is a causal relationship between mortality and NYHA class, since no mortality data are available from the EXPLORER-HCM study. Therefore, the submitting company used NYHA class as an intermediate endpoint. The hazard ratios applied in the base case are taken from a secondary source (Optum Market Clarity study)[13] to supplement the analysis. Given the uncertainty surrounding mortality, the Assessment Team sought to further examine the upper limits of the parameter. In response, the submitting company presented additional scenarios for exploratory purposes. Despite mortality being a key uncertainty, the submitting company's sensitivity analysis adequately addresses the concerns.
- Clinical experts consulted by SMC advised that the introduction of mavacamten would likely have a significant service impact. In the base case the costing for CYP2C19 genotyping is not included, however is explored in the scenario analysis using guidance from NICE. This guidance is based on clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack in the NHS in England, where there are still ongoing discussions on the true cost of both laboratory testing and point of care tests. Therefore, the impact of this test on the economic case is uncertain.

*Other data were also assessed but remain confidential.**

7. Conclusion

After considering all the available evidence, the Committee accepted mavacamten for use in NHSScotland.

8. Guidelines and Protocols

In 2023, the European Society of Cardiology (ESC) published the "Guidelines for the management of cardiomyopathies".[3]

In 2020, the American Heart Association and The American College of Cardiology published the "Guidelines for the diagnosis and treatment of patients with hypertrophic cardiomyopathy".[17]

9. Additional Information

9.1. Product availability date

April 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Mavacamten hard capsules	**Weeks 1 to 12:** **Starting dose of 2.5 mg or 5 mg once daily, though dose reductions/interruptions can occur at weeks 4 and 8.** **Week 12 onwards (every 12 weeks):** **Dose can be between 2.5 mg once daily to 15 mg once daily (see SPC for more details).**	**Weeks 1 to 12 (assuming no dose adjustments/interruptions during this period): £3,219.60** **Week 12 onwards (assuming no dose adjustments/interruptions during this period): £10,732.00**

Costs from BNF online on 08 Jan 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 13 February 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the

individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.