# NCPE Assessment

# Technical Summary

## Mavacamten (Camzyos®)

## HTA ID: 23028

January 2025

Applicant: Bristol-Myers Squibb

Mavacamten for the treatment of symptomatic (New York Heart Association, NYHA, class II to III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of mavacamten (Camzyos®).

Following assessment of the Applicant's submission, the NCPE recommends that mavacamten (Camzyos®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Bristol-Myers Squibb) Health Technology Assessment of mavacamten (Camzyos®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

**About the National Centre for Pharmacoeconomics**

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

## Summary

In December 2023, the Applicant (Bristol-Myers Squibb) submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of mavacamten (Camzyos®) for the treatment of symptomatic (New York Heart Association, NYHA, class II to III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients. There are four NYHA classes. Severity of symptoms increases as NYHA class number increases. A reduction in NYHA class represents an improvement in symptoms. The Applicant is seeking reimbursement of mavacamten on the High-Tech Drug Arrangement.

Mavacamten is a selective, allosteric, and reversible cardiac myosin inhibitor. It targets the underlying myofibrillar disarray and abnormal mitral apparatus that contribute to left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. It is formulated as a hard capsule, for oral administration, and is available in four strengths: 2.5mg, 5mg, 10mg, and 15mg. Patients should be genotyped for cytochrome P450 2C19 (CYP 2C19), prior to treatment initiation, to determine the appropriate dose. The recommended dose range is between 2.5mg and 15mg once daily depending on patient CYP2 C19 metaboliser phenotype. Treatment is potentially for life. Consideration should be given to discontinuing mavacamten in patients who have shown no response after four to six months on the maximum, appropriate, tolerated dose.

Mavacamten also reduces left ventricular ejection fraction (LVEF). Therefore, patients initiated on mavacamten require additional monitoring. If at any visit LVEF is less than 50%, treatment with mavacamten should be interrupted for at least four weeks and until LVEF returns to 50% or greater.

Guidelines from the European Society of Cardiology and the American Heart Association recommend that mavacamten be prescribed for the treatment of oHCM in adult patients who remain symptomatic despite treatment with a beta-blocker (BB) or calcium channel blocker (CCB). This positioning is supported by Clinical Opinion to the NCPE Review Group. In this setting, mavacamten would be prescribed in addition to BB or CCB.

The Review Group note that disopyramide is also used, in Ireland, to treat patients who are

refractory to BB or CCB. However, disopyramide was not included as a comparator to mavacamten. The Review Group considered this to be a limitation of the assessment.

## 1. Comparative effectiveness of mavacamten

Clinical evidence informing the efficacy of mavacamten, for the treatment of symptomatic (NYHA class II to III) oHCM in adult patients, comes from the EXPLORER-HCM trial. EXPLORER-HCM was a phase III, international, double-blind, randomised, placebo-controlled trial. It compared the efficacy and safety of mavacamten (n=123) versus placebo (n=128) up to 30 weeks of treatment. Eligible participants were adults with symptomatic (NYHA class II or III) oHCM, and who had LVEF ≥ 55%. Participants established on BB or CCB monotherapy for treatment of oHCM (92% of participants) were permitted to continue treatment. Continuation of disopyramide was not permitted due to the risk of additive negative inotropic effects if taken concomitantly with mavacamten. The primary efficacy composite endpoint was clinical response at 30 weeks compared with baseline, defined as an improvement of ≥ 1.5 mL/kg/min in peak oxygen uptake ($pVO_2$) and a reduction of ≥ 1 NYHA class; or an improvement of ≥ 3.0 mL/kg/min in $pVO_2$ with no worsening of NYHA class. Key secondary efficacy endpoints were changes, from baseline to Week 30, in post exercise left ventricular outflow tract (LVOT) peak gradient, in $pVO_2$, and in the proportion of participants with ≥1 NYHA class reduction. In total, 37% of participants in the mavacamten arm compared with 17% in the placebo arm met the primary efficacy composite endpoint; the difference was statistically significant. Mavacamten also demonstrated statistically significant improvements in the key secondary efficacy endpoints. The Review Group identified several limitations of the clinical trial evidence. The majority of patients in the mavacamten arm (63%) did not achieve the primary composite endpoint. Also, there is no evidence to suggest that mavacamten improves mortality or reduces the rate of hospitalisation.

Direct comparative evidence was not available for mavacamten versus disopyramide. The Applicant stated that an indirect treatment comparison was not possible due to a paucity of published evidence for disopyramide. The omission of disopyramide as a comparator was considered to be an important limitation of this assessment.

## 2. Safety of mavacamten

During the 30-week blinded treatment period in EXPLORER-HCM, the proportion of participants who reported a treatment-emergent adverse event (AE) was 88% and 79% for the mavacamten and placebo arms, respectively. The most commonly reported AEs across both arms were dizziness (17% (mavacamten) vs 12% (placebo)), dyspnoea (7% vs 8%) and nasopharyngitis (11% vs 12%). Atrial fibrillation was reported by two participants in the mavacamten arm, and by four participants in the placebo arm. A total of nine participants (3.6%) experienced a transient decrease in LVEF to < 50%: seven (5.7%) in the mavacamten arm and two (1.6%) in the placebo arm.

Mavacamten may cause heart failure due to systolic dysfunction defined as symptomatic LVEF < 50%. The risk of mavacamten-induced heart failure is greater in individuals with CYP2 C19 poor metaboliser phenotype; or in patients prescribed concomitant medicines that are inhibitors of CYP 2C19, or strong to moderate inhibitors of CYP 3A4. Risk Management plans have been implemented by both the European Medicines Agency and the Food and Drug Administration.

## 3. Cost effectiveness of mavacamten

### Methods

Cost-effectiveness was assessed, from the perspective of the HSE, using a Markov state transition model developed in Microsoft® Excel. The population considered in the model was adult patients with symptomatic (NYHA class II or III) oHCM. The intervention was mavacamten with BB or CCB therapy (mavacamten+BB/CCB). The comparator was BB or CCB monotherapy (BB/CCB monotherapy).

The model comprised five mutually exclusive health states: NYHA classes I, II, III IV, and Death. Patients entered the model via the NYHA class II or NYHA class III health state. During the first 30 weeks, cycle lengths were either 14 or 28 days in duration (as aligned with clinical assessment time points from EXPLORER-HCM). After 30 weeks, cycle length was 28 days. A half-cycle correction was applied. A lifetime horizon was modelled.

At each cycle patients could either remain in the NYHA health state, transition to any other NYHA class health state or to the Death state. In the Applicant base case, treatment-specific transition probabilities, derived from EXPLORER-HCM, informed movement between NYHA health states up to Week 30 for mavacamten+BB/CCB and up to Week 46 for BB/CCB

monotherapy. The Review Group note that using efficacy data to inform different time points, for the intervention and comparator, could bias results. No additional treatment effect was modelled after the end of the 30-week double-blind treatment period in EXPLORER-HCM. Instead, an annual disease progression rate of 4.55% was used to inform transition of patients to subsequent, less favourable, NYHA classes.

The Applicant identified three real-world evidence studies to inform mortality in the model. One was used to inform mortality in the Applicant base case; the remaining were presented as scenario analyses. The model was sensitive to assumptions in mortality.

Patients were assumed to remain on mavacamten+BB/CCB for life unless discontinuation criteria were met. Discontinuation was not permitted for either mavacamten+BB/CCB or BB/CCB monotherapy before Week 30 in the model. Assumptions in the model regarding discontinuation of mavacamten+BB/CCB included that 1.6% of patients would discontinue at Week 30 due to serious adverse events (SAEs); any patient who was not in a more favourable NYHA class at Week 30, compared to baseline, would discontinue at Week 30 (100% patients in NYHA class III and 63.5% of patients in NHYA class II); after Week 30, 2.77% of patients remaining on treatment would discontinue annually due to SAEs; and after Week 30, patients remaining on mavacamten+BB/CCB would discontinue treatment immediately if they transitioned to a less favourable NYHA class health state. The Review Group considered the assumptions regarding discontinuation to be uncertain.

Patients who discontinued mavacamten+BB/CCB were assumed to receive BB/CCB monotherapy in the subsequent cycle and, thereafter were subject to the same modelling assumptions as patients in the comparator arm. After Week 30, and at each subsequent cycle, patients in the BB/CCB monotherapy arm could either remain on treatment or escalate to subsequent therapies, which were modelled as a sequence of treatments. At each cycle, an NYHA class-specific proportion of patients escalated to subsequent therapy. The first escalation was from BB/CCB monotherapy to disopyramide in combination with BB/CCB, followed by a subsequent escalation to septal reduction therapy (SRT). SRT was modelled as an incident event. Following SRT, patients moved to a post-SRT state. After one cycle they then reverted back to BB/CCB monotherapy.

A systematic literature review identified health related quality of life data collected from

EXPLORER-HCM as the most appropriate to inform health state utility values. Data collected using the EQ-5D-5L instrument was converted to EQ-5D-3L using the Hernandez-Alva algorithm. A limitation of the data was the small number of observations collected from patients in NYHA class IV. It was assumed that patients in NYHA class IV had the same utility as patients in NYHA class III.

Costs and resources included were drug acquisition costs, additional monitoring costs for mavacamten, and AE costs. Healthcare resources included hospitalisations, outpatient appointments, primary care visits and emergency department visits. A once-off, end-of-life cost was also included for patients who entered the Death state.

### Results

Several changes were made to inform the NCPE adjusted base case. Treatment efficacy data from EXPLORER-HCM was used to inform transition probabilities up to 30 weeks for both mavacamten+BB/CCB and BB/CCB monotherapy. The assumption of long-term annual discontinuation of mavacamten+BB/CCB due to SAEs was removed. Data from an alternative study provided by the Applicant was used to inform mortality; this was supported by clinical opinion received by the Review Group. Results of the Applicant and NCPE adjusted base case deterministic cost-effectiveness analyses are presented in Tables 1 and 2, respectively.

**Table 1: Applicant base case incremental cost-effectiveness results [a]**

| Treatments | Total costs (€) | Total QALYs | Incremental costs (€) | Incremental QALYs | ICER (€/QALY) |
|---|---|---|---|---|---|
| Mavacamten+BB/CCB | 144,323 | 9.48 | - | - | - |
| BB/CCB monotherapy | 53,005 | 8.17 | 91,317 | 1.31 | 69,727 |

**BB**: beta blocker; **CCB:** calcium channel blocker; **ICER:** incremental cost-effectiveness ratio; **PAS:** patient access scheme; **QALY:** quality-adjusted life year

[a] Corresponding probabilistic ICER using 1,000 iterations =€69,855 per QALY.
[b] The Applicant has proposed a PAS for mavacamten, not reflected in this table.
Total costs and QALYs presented are discounted (4%). Figures in the table are rounded; calculations may not be directly replicable.

**Table 2: NCPE adjusted base case incremental cost-effectiveness results [a]**

| Treatments | Total costs (€) | Total QALYs | Incremental costs (€) | Incremental QALYs | ICER (€/QALY) |
|---|---|---|---|---|---|
| Mavacamten + BB/CCB | 169,787 | 9.82 | - | - | - |
| BB/CCB monotherapy | 54,489 | 9.00 | 115,298 | 0.82 | 139,897 |

**BB:** beta blocker; **CCB:** calcium channel blocker; **ICER:** incremental cost-effectiveness ratio; **NCPE:** National Centre for Pharmacoeconomics; **PAS:** patient access scheme; **QALY:** quality adjusted life year

[a] Corresponding probabilistic ICER using 1,000 iterations =€140,904 per QALY.
[b] The Applicant has proposed a PAS for mavacamten, not reflected in this table.
Total costs and QALYs presented are discounted (4%). Figures in the table are rounded; calculations may not be directly replicable.

### Sensitivity analysis

Deterministic one-way sensitivity analysis indicated that the most influential parameters, in the Applicant base case, were long-term annual discontinuation of mavacamten+BB/CCB (after Week 30) due to SAEs, and mortality. The most influential parameters, in the NCPE adjusted base case, were annual disease progression and mortality.

The probability of cost-effectiveness, at both the €20,000 and €45,000 per quality adjusted life year (QALY) thresholds, was 0% for both the Applicant and NCPE-adjusted base case. A price-ICER analysis, using NCPE-adjusted base case assumptions, indicated that reductions of 77% and 95% (including the Framework Agreement rebate) would be required to meet the €45,000 per QALY and €20,000 per QALY cost-effectiveness thresholds.

### Change to mavacamten monitoring requirements

On 14 January 2025, the European Medicines Agency updated the summary of product characteristics for mavacamten to describe a change in monitoring requirements. The NCPE adjusted base case incremental cost-effectiveness ratio (ICER) decreases to €133,164 per QALY when this change is incorporated.

## 4. Budget impact of mavacamten

The price to wholesaler per pack (28 capsules) of mavacamten is €1,318.64; this is the same for all strengths. The annual cost, per patient, to the HSE (incorporating mark-up, Framework Agreement rebate, and High Tech Arrangement patient care fees) is €17,785. Value added tax is not applicable to oral medicines.

It was assumed that mavacamten would be used in line with Guidelines and Clinical Opinion. Published literature informed the population estimates. Several of the inputs are uncertain. The Applicant estimated that 57 patients would be treated with mavacamten in Year One, increasing to 465 in Year Five. The Applicant-estimated cumulative five-year gross drug budget impact was approximately €28.9 million. The assumption of long-term annual discontinuation of mavacamten due to SAEs was included in the Applicant budget impact analysis. The Review Group removed this assumption to inform NCPE adjusted estimates. The NCPE-adjusted estimate was €29.8 million. However, the Review Group consider that discontinuation continued to be overestimated by other assumptions made in the model. In clinical practice, and in the absence of a control measure, it is unlikely that mavacamten discontinuation will be as frequent or as immediate as that suggested by the Applicant.

Therefore, budget impact figures may be underestimated. The implementation of a managed access programme would be recommended if a decision was made to reimburse mavacamten. In this setting, mavacamten is given in addition to BB/CCB and the net budget impacts are the same as the respective gross budget impacts.

The Review Group note that packs are flat priced regardless of capsule strength. An assumption of the cost-effectiveness and budget impact analyses is that patients are dispensed one pack of the appropriate strength of mavacamten every 28 days. If, however, for example, a patient prescribed 15mg mavacamten once daily was dispensed three boxes of the 5mg strength once every 28 days, the associated cost for that patient would triple. This would impact both the cost-effectiveness and budget impact.

## 5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

## 6. Conclusion

The NCPE recommends that mavacamten not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*