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CADTH Reimbursement Recommendation

Mavacamten (Camzyos)

Indication: For the treatment of symptomatic obstructive hypertrophic cardiomyopathy of New York Heart Association class II to III in adult patients

Sponsor: Bristol Myers Squibb

Final recommendation: Reimburse with conditions

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

What Is the CADTH Reimbursement Recommendation for Camzyos?

CADTH recommends that Camzyos be reimbursed by public drug plans for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) of New York Heart Association (NYHA) class II to III in adult patients if certain conditions are met.

Which Patients Are Eligible for Coverage?

Camzyos should only be covered to treat patients who have a documented left ventricular ejection fraction (LVEF) of 55% or greater at rest, determined by echocardiography, a left ventricular (LV) wall thickness of 15 mm or more (or ≥ 13 mm with a family history of hypertrophic cardiomyopathy [HCM]), and a left ventricular outflow tract (LVOT) peak gradient of 50 mm Hg or greater at rest, after Valsalva maneuver, or postexercise as confirmed by echocardiography. To be eligible, patients must also experience either worsening of symptoms or echocardiographically demonstrated deterioration while taking a beta-blocker (BB) or calcium channel blocker (CCB).

What Are the Conditions for Reimbursement?

Camzyos should only be reimbursed if patients are under the care of a cardiologist and if the cost of Camzyos is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from the EXPLORER-HCM clinical trial demonstrated that NYHA class and peak oxygen consumption (pVO_2) improved in patients with symptomatic oHCM who were treated with Camzyos. Evidence from the VALOR-HCM clinical trial demonstrated that fewer patients treated with Camzyos met the criteria for septal reduction therapy (SRT) or chose to have the procedure.
- Camzyos may address some of the needs that are important to patients by reducing HCM symptoms and improving patients' health-related quality of life (HRQoL).
- Based on CADTH's assessment of the health economic evidence, Camzyos does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Camzyos is estimated to cost the public drug plans approximately $54 million over the next 3 years.

Summary

Additional Information

What Is oHCM?

HCM is a genetic heart disease that occurs in about 1 in 500 adults and causes increased heart muscle thickness, making it difficult for the heart to pump blood. In oHCM, the thickened part of the heart muscle blocks or reduces the blood flow from the LV to the rest of the body. Associated complications of oHCM include heart failure, stroke, arrhythmias, and sudden cardiac death.

Unmet Needs in oHCM

Patients with oHCM identified a need for treatment options that reduce the risk of heart failure, sudden cardiac death, and the debilitating symptoms that affect their daily living activities and quality of life. Patients also expressed a need for treatments that are noninvasive alternatives to SRT, target the underlying cause of HCM, potentially reverse the course of the disease, and are more efficacious than currently available treatments.

How Much Does Camzyos Cost?

Treatment with Camzyos is expected to cost approximately $22,484 per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that mavacamten be reimbursed for the treatment of symptomatic oHCM of NYHA class II to III in adult patients only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase III, randomized, double-blind, placebo-controlled trials (EXPLORER-HCM [n = 251] and VALOR-HCM [n = 112]) demonstrated that treatment with mavacamten resulted in added clinical benefit in adult patients with symptomatic oHCM. In the EXPLORER-HCM trial, mavacamten was statistically significantly more efficacious than placebo in improving the NYHA class and exercise capacity (pVO_2) in patients with symptomatic oHCM of NYHA class II to III. Results of the primary composite outcome showed that 37% of patients on mavacamten versus 17% of patients on placebo met the primary end point at week 30, with a between-group difference of 19.4%, (95% confidence interval [CI], 8.7 to 30.1; P = 0.0005). Compared to patients in the placebo group, those in the mavacamten group also had greater reductions in postexercise LVOT gradient, with a mean difference of −36 mm Hg (95% CI, −43.2 to −28.1; P < 0.0001); greater increases in pVO_2, with a mean difference of 1.4 mL/kg per min (95% CI, 0.6 to 2.1; P = 0.0006); and improvements by 1 or more NYHA functional classes (65% of patients in the mavacamten group versus 31% of patients in the placebo group), with a between-group difference of 34% (95% CI, 22.2 to 45.4; P < 0.0001). Patients treated with mavacamten also reported greater improvement in HRQoL, as assessed by the scores on the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ CSS), with a mean difference of 9.1 (95% CI, 5.5 to 12.7; P < 0.0001), and greater reductions in severity of HCM symptoms as assessed by the Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath (HCMSQ SoB) domain score, with a mean difference of −1.8 (95% CI, −2.4 to −1.2; P < 0.0001). The VALOR-HCM study was conducted in patients with symptomatic oHCM of NYHA class III to IV or class II with exertional syncope or near syncope. In this study, the results of the primary composite outcome showed that at week 16, 17.9% of patients receiving mavacamten continued to meet guideline criteria for being eligible for SRT or elected to undergo the procedure compared to 76.8% of patients receiving placebo, with a treatment difference of 58.9% (95% CI, 44.0% to 73.9%; P < 0.001). Compared to patients in the placebo group, patients in the mavacamten group also had a greater reduction in postexercise LVOT gradient, with a mean difference of −37.2 mm Hg (95% CI, −48.1 mm Hg to −26.2 mm Hg; P < 0.001); improvements by 1 or more NYHA functional class, with a between-group difference of 41.1% (95% CI, 24.5% to 57.7%; P < 0.001); and greater improvement in HRQoL, as assessed by the KCCQ CSS, with a mean difference of 9.4 points (95% CI, 4.9 points to 14.0 points; P < 0.001). Although the place in therapy of mavacamten for the management of oHCM is not completely clear, CDEC considered that mavacamten is an additional second-line treatment option after BBs or CCBs.

Patients identified a need for treatment options that reduce the risk of heart failure and sudden cardiac death, as well as the debilitating symptoms that affect daily living activities and quality of life. Patients also expressed a need for treatments that are better noninvasive alternatives to SRT, that target the underlying cause of HCM, that potentially reverse the course of the disease, and that are more efficacious. Patients

identified a particular need for additional options for those who cannot tolerate the side effects of BBs and CCBs. CDEC concluded that based on the evidence, mavacamten appears to address some of the needs identified by patients, by reducing HCM symptoms and improving patients' HRQoL.

Using the sponsor-submitted price for mavacamten and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for mavacamten when added to BBs or CCBs was $576,295 per quality-adjusted life-year (QALY) compared with BBs or CCBs alone. At this incremental cost-effectiveness ratio, mavacamten is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for adult patients with symptomatic oHCM of NYHA class II to III. A price reduction is required for mavacamten to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. In patients with all the following: 1.1. documented LVEF ≥ 55% at rest determined by echocardiography 1.2. LV wall thickness ≥ 15 mm (or ≥ 13 mm with a family history of HCM) 1.3. LVOT peak gradient ≥ 50 mm Hg at rest, after Valsalva maneuver, or postexercise, as confirmed by echocardiography.	Patients enrolled in the EXPLORER-HCM and VALOR-HCM trials had to have an LVEF of at least 55% and 60% at screening, respectively. In addition, patients enrolled in both studies had to have an LV wall thickness of ≥ 15 mm (or ≥ 13 mm with a family history of HCM); an LVOT peak gradient ≥ 50 mm Hg at rest, after Valsalva maneuver, or postexercise, as confirmed by echocardiography; and adequate acoustic windows to enable accurate TTEs.	LVEF must be measured via echocardiography.
2. Patients must be receiving BB or CCB therapy and experience clinical deterioration in symptoms or echocardiography while receiving either of these treatments.	The majority of patients (90%) enrolled in the EXPLORER-HCM and VALOR-HCM trials were on some form of background therapy with a BB or CCB.	Based on clinical expert opinion, clinical deterioration should be defined as either worsening of symptoms or echocardiographically demonstrated deterioration in outflow tract obstruction.
Discontinuation		
3. Mavacamten should be permanently discontinued if the patient has either: 3.1. LVEF ≤ 30% 3.2. receives SRT.	In both the EXPLORER-HCM and VALOR-HCM trials, treatment with mavacamten was permanently discontinued if LVEF decreased to 30% or less. No evidence was identified to demonstrate an efficacy or safety benefit of mavacamten in patients who have undergone SRT.	LVEF must be measured via echocardiography. The product monograph also states that mavacamten should be discontinued if an LVEF < 50% occurs on 2 consecutive occasions with 2.5 mg daily.

Reimbursement condition	Reason	Implementation guidance
Prescribing		
4. The patient should be under the care of a cardiologist.	Accurate diagnosis and follow-up of patients with oHCM is important to ensure that mavacamten is prescribed to the most appropriate patients.	—
Pricing		
5. A reduction in price	The ICER for mavacamten plus a BB or CCB is $576,295 when compared with a BB or CCB alone. A price reduction of at least 73% for mavacamten would be required for mavacamten plus a BB or CCB to achieve an ICER of $50,000 per QALY gained compared to BBs or CCBs alone.	—

BB = beta-blocker; CCB = calcium channel blocker; HCM = hypertrophic cardiomyopathy; ICER = incremental cost-effectiveness ratio; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; oHCM = obstructive hypertrophic cardiomyopathy; QALY = quality-adjusted life-year; SRT = septal reduction therapy; TTE = transthoracic echocardiography.

Discussion Points

- CDEC members discussed that symptomatic oHCM is a chronic disease and that while descriptive results for the VALOR-HCM trial are available through to week 32, it is uncertain if mavacamten can reduce the need for SRT among patients with symptomatic oHCM in the long term. Furthermore, there is no direct evidence of mavacamten compared to SRT available. In addition, it is unknown what impact mavacamten will have on the natural history of the disease.
- Given that mavacamten was evaluated in the EXPLORER-HCM trial as an add-on to first-line treatment of BB or CCB therapy, CDEC discussed the clinical efficacy of mavacamten as a first-line therapy, but there is no evidence available for the use of mavacamten as a first-line therapy; in addition, there is limited evidence for the addition of mavacamten to BBs or CCBs plus disopyramide. Hence, CDEC recommended that mavacamten be prescribed as a second-line treatment after patients demonstrate clinical deterioration while taking a BB or CCB therapy.
- CDEC discussed that while the clinical practice guidelines recommend disopyramide as a second-line treatment for patients with symptomatic oHCM, the clinical expert noted that disopyramide is not widely used in clinical practice in Canada given concerns that disopyramide may increase the QT interval on the electrocardiograph, likely requiring first doses to be administered in hospitals and emergency departments, with all the attendant resource consequences.
- CDEC discussed that there is a limited number of centres in Canada that conduct SRT, that SRT is associated with potentially severe complications, as well as the potential need for pacemaker implantation and reintervention, and that mavacamten could potentially improve oHCM symptoms and delay the time until SRT is required.
- The estimated price reduction required to achieve cost-effectiveness is uncertain. The long-term efficacy of mavacamten is highly uncertain given the lack of clinical data available to support the

modelled long-term relative benefit of mavacamten plus a BB or CCB compared with BBs or CCBs alone. If the long-term relative effectiveness of mavacamten plus a BB or CCB compared to BBs or CCBs is worse than predicted, a greater price reduction will be required for mavacamten to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained.

- CDEC noted that clinical expert believes that patient registries for oHCM would be of great value as there are still evidence gaps and the therapeutic pathways are still unclear. Jurisdictions may want to discuss with the sponsor the need for a registry for patients with oHCM.

Background

HCM is a common genetic heart disease characterized by increased LV wall thickness. About 30% to 60% of patients with HCM have identifiable familial disease caused by mutations in cardiac sarcomere protein genes and each offspring of an affected family member has a 50% chance of inheriting the altered gene, although not all family members who inherit an HCM mutation will develop the disease. The distribution of HCM is equal by sex, although women have been diagnosed less frequently than men. The age of symptom onset and the severity of symptoms varies significantly across patients. Among those with HCM who do develop symptoms, the most common ones include chest pain, shortness of breath with exertion, fatigue, palpitations, and lightheadedness. oHCM, a subclassification of HCM, is characterized by LVOT obstruction, with the obstruction impeding blood flow from the heart to the rest of the body, defined in the 2020 American Heart Association/American College of Cardiology (AHA/ACC) clinical guidelines as a peak LVOT gradient 30 mm Hg or higher. Patients with oHCM are more likely to develop symptoms such as increased myocardial wall stress, myocardial ischemia, and eventually, cell death and replacement scarring. Associated complications include heart failure, stroke due to atrial fibrillations, arrhythmias, and sudden cardiac death. The estimated prevalence of HCM in the general population is 1 in 500 adults, although most of these cases remain undiagnosed. The 2020 AHA/ACC clinical guidelines suggest that oHCM is present or develops over time in most patients with HCM, with about a third diagnosed with nonobstructive HCM. Estimates for the proportion of patients with HCM who have oHCM ranges from 22% in a study from western Sweden to 70% in a US study.

Mavacamten is a first-in-class cardiac myosin inhibitor. Mavacamten modulates the number of myosin heads that can enter power-generating states, reducing force-producing systolic and residual diastolic cross-bridge formation. Mavacamten also shifts the overall myosin population toward an energy sparing, recruitable, superrelaxed state.

This is the first CADTH review for mavacamten. The Health Canada indication is for the treatment of symptomatic oHCM of NYHA class II to III in adult patients. Mavacamten is available as a 2.5 mg, 5 mg, 10 mg, or 15 mg capsule. The product monograph-recommended starting dose of mavacamten for oHCM is 5 mg orally once daily. Patients should be assessed 4 weeks after initiation to for a clinical response. If LVOT gradient with Valsalva maneuver is less than 20 mm Hg, the dose should be decreased to 2.5 mg once daily. Otherwise, 5 mg once-daily dosing should be maintained. Thereafter, follow-up visits should occur at 8 weeks and 12 weeks after treatment initiation, with dose adjustments as appropriate. The product monograph for

mavacamten contains serious warnings and precautions regarding the risk of heart failure and notes that mavacamten reduces LVEF and can cause heart failure due to systolic dysfunction, and that echocardiogram assessments of LVEF and LVOT gradient are required before, and regularly during, treatment with mavacamten. It also notes that initiation of mavacamten in patients with an LVEF of lower than 55% is not recommended and that mavacamten treatment should be interrupted if LVEF is lower than 50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status. The product monograph also states that concomitant use of mavacamten in patients on combination therapy of a CCB (e.g., verapamil, diltiazem) and a BB should be avoided.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 randomized controlled trials in adult patients with oHCM
- patient perspectives gathered by 2 patient groups, the Canadian Heart Patient Alliance (CHPA) and the HeartLife Foundation
- input from public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with cardiovascular disease
- input from 2 clinician groups, including a community-based cardiology clinic, Cardio1, and an independent cardiologist
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient advocacy groups, the CHPA and the HeartLife Foundation, provided input for the treatment of symptomatic oHCM in adult patients. One patient group, HeartLife Foundation, gathered information from in-depth interviews with expert physicians and patients across Canada, and a review of study material and online literature. Another group (the CHPA) conducted extensive interviews with 3 clinicians (2 in the US and 1 in Italy) involved with clinical trials for mavacamten. They also gathered information through meeting with staff from the US-based Hypertrophic Cardiomyopathy Association, as well as from reviewing recorded panel discussions, patient testimonials, and educational videos. The CHPA recruited participants through the US-based clinicians as well as outreach through the database for the CHPA in Canada, with additional patient profiles and confirmatory information provided by the Hypertrophic Cardiomyopathy Association. A total of 16 patient responses were gathered; among them, 62.5% were female (10 out of 16), aged between mid-30s and mid-70s, and 31% (5 out of 16) were identified as people in Canada (1 living in US), and 69% (11 respondents) as people in the US. All participants reported being diagnosed with oHCM, and 40% also identified as diagnosed with NYHA functional class II and 40% with NYHA functional class III. About 25% of

participants mentioned being diagnosed with atrial fibrillation. Among the 16 respondents, 4 patients had been treated with mavacamten, all of whom were residents in the US.

Both patient groups agreed that HCM has a negative impact on patients' quality of life. The impacts of delayed diagnosis and misdiagnosis, shortness of breath, exercise intolerance, arrythmia, palpitations, chest pain, fatigue, and fainting were some of the major issues experienced by the respondents. One patient group also mentioned HCM affecting patients' families and friends both mentally and physically. While describing their experiences with currently available drugs, participants reported experiencing a variety of treatments, including heart surgery, implantable cardioverter defibrillators, alcohol septal ablation, and a variety of medications (such as BBs, CCBs, and antiarrhythmics). However, both patient groups reported concerns from both patients and health care providers regarding current treatments, and patients' symptoms and feelings of uncertainty and unresolved anxiety with the available treatment options.

While evaluating improved outcomes from new treatments, patients expressed a desire to see a reduction in the risk of heart failure, including sudden death as a current unmet need, as well as reductions in the debilitating symptoms affecting daily living activities and quality of life, including shortness of breath, irregular heartbeat, palpitations, chest pain, fatigue, stress, and anxiety. Moreover, spending time with loved ones, the ability to go to work on a regular basis, pursuing outdoor activities, and the ability to travel were some of the quality-of-life indicators and experiences patients and caregivers mentioned.

While describing their experiences with the current drug under review, 4 patients recruited by the CHPA reported "very positive" experiences, noting that they have more energy to perform daily tasks and they were hopeful that the drug will reduce their symptoms and risk of cardiac arrest. The HeartLife Foundation described findings from a Cleveland Clinic–led clinical trial (VALOR-HCM) demonstrating a reduced need for an invasive procedure like SRT in patients who have severely symptomatic oHCM when mavacamten was used. However, the CHPA reiterated the need to assess patients' cardiac statuses, specifically by echocardiogram of LVEF, as well as other illnesses (e.g., infections or chronic disease), other cardiovascular symptoms (arrhythmias), and other medications before the approval for mavacamten. Moreover, patients must be closely monitored with echocardiogram for the first few months, as well as on a regular basis (every 3 months), and report any symptoms because of the risk of heart failure associated with mavacamten. The CHPA mentioned that this limits the prescription of mavacamten to patients who have access to a high-volume clinic and are committed to regular monitoring and reporting of symptoms.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

According to the clinical expert, for patients with symptomatic oHCM, standard treatment has aimed to lessen the extent of LVOT obstruction and manage arrhythmias. BBs have been the traditional mainstay of therapy. Where BBs cannot be used or are not tolerated, non-dihydropyridine CCBs, diltiazem or verapamil, can be prescribed. Should symptoms persist, then disopyramide is recommended as add-on therapy. These drugs, taken separately or in combination, improve symptoms and quality of life. According to the clinical

expert consulted, mavacamten may meet an unmet need as an add-on therapy for patients not experiencing symptom relief with BBs or CCBs with or without disopyramide.

The clinical expert consulted for this review noted that mavacamten has been evaluated in the EXPLORER-HCM study as an add-on to first-line treatment of BB or CCB therapy in the context of improving symptoms and exercise capacity among patients with symptomatic oHCM. In terms of treatment paradigm, the clinical expert stated that mavacamten will provide another treatment option for symptomatic patients with oHCM. In their opinion, the current place in therapy for mavacamten is unclear. It may be as an add-on to BBs or CCBs, or more appropriately as a third-line drug as an add-on to BBs or CCBs plus disopyramide. The fact that mavacamten was not tested head-to-head with disopyramide raises uncertainty as to its relative position in the treatment algorithm, according to the expert. They also stated that while it has its own issues, disopyramide is a class I antiarrhythmic with negative inotropic properties that have been argued to be more powerful than BBs or CCBs in controlling LVOT obstruction.

According to the clinical expert, patients with symptomatic oHCM whose disease has not sufficiently responded to their current treatment and/or whose symptoms are worsening would be eligible for treatment with mavacamten. Patients would need to be sufficiently symptomatic to need the drug (i.e., at least NYHA class II) despite treatment with BBs or CCBs with or without disopyramide. According to the expert, the metrics of response to treatment with mavacamten include stabilization or improvement of symptoms (e.g., fatigue, palpitations, lightheadedness, and chest pain), reduction in the frequency and/or severity of symptoms, and improved ability to perform activities of daily living. In the opinion of the clinical expert, treatment should be discontinued if drug side effects were to occur. If symptoms or LVOT gradient were to progress to the point that SRT was needed, then treatment with mavacamten should be discontinued. According to the clinical expert, mavacamten should be prescribed by specialists (cardiologists) or in specialty clinics.

Clinician Group Input

Clinician group input on the review of mavacamten for the treatment of oHCM was received from 2 clinician groups: a community-based cardiology clinic called Cardio1, and an independent cardiologist who is a member of the HCM Clinic at the University of Calgary, the Stephenson Cardiac Imaging Center, and the Libin Cardiovascular Institute at the University of Calgary.

The clinician groups mentioned that BBs, CCBs, and disopyramide are current treatments for oHCM. However, use of these treatments is for symptom management as they do not modify the underlying disease. There are also potential adverse effects associated with these drugs, which limit their use. Cardio1 also pointed out that SRTs, like surgical and percutaneous septal ablation, may be beneficial to those who are refractory to drugs. However, they also have potential adverse effects and limitations and require proper and careful selection of patients, indicating an unmet medical need for better noninvasive alternatives to SRT.

There remains some unmet needs when current treatment options are deemed ineffective, are unable to reverse the course of the disease, and are used mostly for symptom relief. While both groups mentioned data and studies showing the effectiveness of the drug under review in improving symptoms and reducing

the need for surgery, Cardio1 focused on using available conventional therapy first and switching to the new therapy when conventional ones fail. The group also put importance on proper selection of patients, as well as checking for updates regarding long-term studies on the use of this new drug. The group added the need for timely assessment of patients' responses to conventional treatments and switching to new treatments to prevent unnecessary suffering.

Regarding best-suited patients for the new medication, 1 group identified patients with oHCM with severe LVOT obstruction who are highly symptomatic as the most suitable candidates, whereas Cardio1 mentioned patients unresponsive to currently available drug treatment as good candidates for this drug, as well as those who may not be a candidate for early SRT, those who want to delay SRT, or those who do not want SRT. While 1 group mentioned its eagerness to offer the new medication to patients, referring to the compelling data behind the new medication, Cardio1 pointed out the ongoing importance of monitoring the mortality, morbidity, and hospitalization outcomes of this drug.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for mavacamten:

- relevant comparators
- considerations for initiation of therapy
- considerations for prescribing of therapy.

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
In clinical practice, what is the typical treatment cascade for patients with oHCM?	The clinical expert noted to CDEC that patients diagnosed with symptomatic oHCM begin treatment with BBs or non-dihydropyridine CCBs as first-line therapy. Patients who cannot tolerate, or whose disease does not respond to, first-line therapy are candidates for disopyramide in combination with BBs or non-dihydropyridine CCBs. Among patients in whom symptoms persist, SRT may be a treatment option.
Should mavacamten replace disopyramide as a combination therapy with a BBs or CCBs or should it be used after a patient has tried combination therapy with disopyramide?	CDEC agreed with the clinical expert consulted by CADTH that the evidence as presented is for the use of mavacamten as an add-on to BBs or CCBs. There is also limited evidence for the addition of mavacamten to BBs or CCBs plus disopyramide. The current place in therapy for mavacamten is unclear. It may be as an add-on to BBs or CCBs, or perhaps more appropriately as a third-line drug, given on top of BBs or CCBs plus disopyramide. The fact that mavacamten was not tested head-to-head with disopyramide raises uncertainty as to its relative position in the treatment algorithm.

Implementation issues	Response
Is there a role for mavacamten monotherapy?	CDEC agreed with the clinical expert consulted by CADTH that there is no role for mavacamten monotherapy.
Mavacamten is a cardiac myosin inhibitor, which reduces the number of actin myosin cross bridges, which attenuates excessive contractility and improves cardiac function. Therefore, isn't it similar to BBs or CCBs in that its function is to address the symptoms of oHCM?	CDEC agreed with the clinical expert consulted by CADTH that mavacamten is similar to BBs or CCBs in terms of the effect of treatment. The clinical expert noted that mavacamten is more specific in its effect on contractility. There are some data showing reverse cardiac remodelling, as well as reductions in LV mass index and LV wall thickness with mavacamten. But whether this ultimately alters disease progression or impacts major clinical outcomes is unknown.
Is there any evidence in the available studies (EXPLORER-HCM, MAVA-LTE, or VALOR-HCM) that reliably demonstrates that mavacamten improves outcomes of oHCM other than symptoms?	CDEC agreed with the clinical expert consulted by CADTH that the duration of the submitted trials were not long enough to reliably demonstrate that mavacamten improves outcomes of oHCM other than symptoms.
Considerations for initiation of therapy	
Are the eligibility criteria for the EXPLORER-HCM trial reasonable for a clinical trial of patients with oHCM? Are the eligibility criteria in the EXPLORER-HCM trial possible to determine in clinical practice (i.e., able to be determined and available across Canada)? Would the eligibility criteria for the trial work as eligibility criteria for reimbursement of mavacamten (as requested by the sponsor)?	The clinical expert noted that patients more clearly eligible for mavacamten are those diagnosed with symptomatic oHCM whose disease does not respond to treatment with disopyramide in combination with BBs or non-dihydropyridine CCBs. CDEC, however, noted that the available evidence does not help answer questions in reference to disopyramide and mavacamten. CDEC agreed with the clinical expert consulted by CADTH that whether mavacamten should replace disopyramide as second-line therapy remains uncertain in the absence of head-to-head trials. This could have been assessed if disopyramide had been used in lieu of placebo in the comparator arm.
If a patient progresses to NYHA class IV, should funding be discontinued?	CDEC agreed with the clinical expert consulted by CADTH that funding should not be discontinued in patients who progress to NYHA class IV, although other treatments, such as SRT, should be under consideration by that point.
Should mavacamten be continued in patients who have undergone SRT?	CDEC agreed with the clinical expert consulted by CADTH that mavacamten should be discontinued in patients who have undergone SRT.
Are the exclusion criteria for the EXPLORER-HCM trial reasonable for a clinical trial of patients with oHCM? Are there any exclusion criteria in the EXPLORER-HCM or other clinical trials that should be used as reimbursement conditions of mavacamten?	CDEC agreed with the clinical expert consulted by CADTH that it is unclear why patients with a history of syncope within 6 months before screening were excluded from the EXPLORER-HCM trial. The clinical expert noted to CDEC that patients with permanent atrial fibrillation who are either not on anticoagulation for more than 4 weeks or not adequately rate controlled for more than 6 months, or any patients with paroxysmal atrial fibrillation present at screening, were excluded in both pivotal trials. The reasoning for this is also unclear. CDEC agreed with the clinical expert consulted by CADTH that the exclusion criteria in the EXPLORER-HCM trial of LVEF of at least 55% should be used as a reimbursement condition of mavacamten.
Considerations for prescribing of therapy	
Do patients with oHCM need to be managed by specialist (e.g., cardiologist), or a specialist with specific training in oHCM?	CDEC agreed with the clinical expert consulted by CADTH that patients with oHCM should preferentially be managed by a cardiologist or specialty clinic. Treatment could be started either on an inpatient

Implementation issues	Response
	or outpatient basis. In regions where no practising cardiologists are available, specialist review and input could be provided virtually.
According to the sponsor's submission, there are only 2 sites in Canada that are established myectomy centres (Toronto General and St. Paul's Hospital in Vancouver). Is this accurate?	According to the clinical expert, these 2 sites are recognized specialty centres and will receive referrals for the more complex cases. However, other centres also perform SRT in Canada.

BB = beta-blocker; CCB = calcium channel blocker; CDEC = CADTH Canadian Drug Expert Committee; LV = left ventricle; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; SRT = septal reduction therapy.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two sponsor-conducted phase III, randomized, double-blind, placebo-controlled trials, EXPLORER-HCM and VALOR-HCM, met the CADTH review protocol criteria and were included in this systematic review.

The EXPLORER-HCM trial (68 sites in 13 countries; N = 251) evaluated the efficacy and safety of once-daily orally administered treatment with mavacamten (starting dose of 5 mg) in adult patients with symptomatic oHCM with an LVOT peak gradient of 50 mm Hg or greater at rest, after Valsalva maneuver, or postexercise; documented LVEF of 55% or greater; a maximum septal wall thickness determined by a core laboratory of 15 mm or greater or ≥ 13 mm or greater with family history of HCM; and with NYHA functional class II or III symptoms. The primary outcome was composite functional response at week 30, defined as achieving an improvement of 1.5 mL/kg/min or more in increase in pVO_2, a 1 or higher NYHA functional class reduction, or a 3.0 mL/kg/min or higher in pVO_2 without NYHA class worsening. Secondary outcomes prespecified in the statistical hierarchy included changes in postexercise LVOT peak gradient, pVO_2, NYHA class, KCCQ CSS, and HCMSQ SoB domain score. Patients had a mean age of 58.5 years (standard deviation = 11.9), most patients (73%) had NYHA functional class II symptoms at baseline, and almost all patients (92%) were on background BB or CCB therapy. Other exploratory outcomes assessed in the EXPLORER-HCM trial that were important to the CADTH review included HRQoL as assessed by the 5-level EQ-5D (EQ-5D-5L) questionnaire, changes in resting and Valsalva LVOT peak gradients, cardiopulmonary exercise testing parameters, cardiac structure, and biomarker-based assessments.

The VALOR-HCM trial (19 sites in the US; N = 112) evaluated the efficacy and safety of once-daily orally administered treatment with mavacamten (starting dose 5 mg) in adult patients with symptomatic oHCM with a dynamic LVOT gradient at rest or with provocation (i.e., Valsalva or exercise) of 50 mm Hg or greater, a documented LVEF of 60% or greater, a maximum septal wall thickness determined by a core laboratory of 15 mm or greater or 13 mm or with family history of HCM, and NYHA functional class III or IV, or class II with exertional syncope or near syncope. Patients must have been referred within the past 12 months for SRT and been actively considering scheduling the procedure. The primary outcome was a composite of the decision to proceed with SRT before or at week 16 or be considered guideline eligible for SRT at week 16. Guideline

eligibility criteria were based on the 2011 ACCF/AHA HCM clinical and hemodynamic criteria. For the primary composite outcome, patients with a maximum LVOT of a 50 mm Hg or greater gradient (from rest, Valsalva, or postexercise) and no improvement in NYHA functional class at week 16 were considered eligible for SRT. Secondary outcomes prespecified in the statistical hierarchy included changes in postexercise LVOT peak gradient, 1 or more classes of NYHA improvement, changes in KCCQ CSS, and changes in N-terminal pro b-type natriuretic peptide (NT-proBNP) and cardiac troponin I biomarkers.

Efficacy Results

Both pivotal trials comparing mavacamten with placebo detected a statistically significant difference in their primary outcomes and all prespecified secondary outcomes were statistically significant in favour of mavacamten.

In the EXPLORER-HCM trial, a total of 37% of patients on mavacamten versus 17% of patients on placebo met the primary end point at week 30 with a between-group difference of 19.4% (95% CI, 8.7 to 30.1; P = 0.0005). In regards to key secondary outcomes tested in the statistical hierarchy from baseline to week 30, patients in the mavacamten group compared to those in the placebo group had greater reductions in postexercise LVOT gradient, with a mean difference of −36 mm Hg (95% CI, −43.2 mm Hg to −28.1 mm Hg; P < 0.0001); greater increases in pVO_2, with a mean difference of 1.4 mL/kg per min (95% CI, 0.6 to 2.1; P = 0.0006), more patients improving by 1 or more NYHA classes (65% of patients in the mavacamten group versus 31% of patients in the placebo group), with a between-group difference of 34% (95% CI, 22.2 to 45.4; P < 0.0001); greater improvement in scores on the KCCQ-23 CSS, with a mean difference of 9.1 (95% CI, 5.5 to 12.7; P < 0.0001); and greater reductions in severity of HCM symptoms, as assessed by the HCMSQ SoB domain score, with a mean difference of −1.8 (95% CI, −2.4 to −1.2; P < 0.0001).

In the VALOR-HCM trial, for the primary composite outcome, after 16 weeks treatment, 17.9% of patients treated with mavacamten continued to meet the guideline criteria for SRT or elected to undergo the procedure compared to 76.8% of patients treated with placebo, with a treatment difference of 58.9% (95% CI, 44.0% to 73.9%; P < 0.001) favouring mavacamten. In regard to key secondary outcomes tested in the statistical hierarchy from baseline to week 16, patients in the mavacamten group compared to those in the placebo group had a greater reduction in postexercise LVOT gradient, with a mean difference of −37.2 mm Hg (95% CI, −48.1 mm Hg to −26.2 mm Hg; P < 0.001), more patients with 1 or more classes of NYHA functional class improvements, with a between-group difference of 41.1% (95% CI, 24.5% to 57.7%; P < 0.001); greater improvement in scores on the KCCQ CSS, with a mean difference of 9.4 points (95% CI, 4.9 points to 14.0 points; P < 0.001); and greater reductions in NT-proBNP and in cardiac troponin I, with geometric mean ratio differences of 0.33 (95% CI, 0.26 to 0.42; P < 0.001) and 0.53 (95% CI, 0.41 to 0.70; P < 0.001), respectively.

Harms Results

In the EXPLORER-HCM trial, through to week 38, a total of 88% of patients in the mavacamten group and 79% of patients in the placebo group experienced 1 or more adverse event (AE). The most common AEs were similar for both treatment groups. The proportion of patients who experienced 1 or more serious adverse event (SAE) was similar between treatment groups (8% versus 9%). A total of 1.6% of patients in

the mavacamten group and 0.8% of patients in the placebo group discontinued treatments due to AEs. No AEs of decreased LVEF were reported; however, incidence of a resting LVEF of less than 50% was a protocol-specified criterion for temporary treatment discontinuation in the EXPLORER-HCM trial. Throughout the 30-week treatment period, 3.6% of patients met temporary treatment discontinuation criteria of a LVEF of lower than 50%, including 5.7% of patients in the mavacamten group and 1.6% of patients in the placebo group. No patients had a reduction in LVEF [redacted] necessitating permanent treatment discontinuation. One death was reported in the placebo group due to sudden death.

In the VALOR-HCM trial, through to week 16, a total of 73.2% of patients in the mavacamten group and 61.8% of patients in the placebo group experienced at least 1 AE. The proportion of patients who had SAEs was similar for the mavacamten and placebo groups (5.4% versus 1.8%). Through to week 16, 3.6% of patients in the mavacamten group had an LVEF of lower than 50%, resulting in temporary drug discontinuation, all of whom subsequently resumed mavacamten dosing. No patients had a reduction in LVEF of 30% or less, necessitating permanent treatment discontinuation through to week 16. There were no reported treatment discontinuations due to AEs or deaths through to week 16.

Critical Appraisal

Internal Validity

Both the EXPLORER-HCM and the VALOR-HCM trials appeared to have acceptable methods for blinding, allocation concealment, and randomization with stratification. The clinical expert consulted for this review stated that the differences in the proportion of patients taking neither BBs nor CCBs at baseline in the EXPLORER-HCM trial (3.3% mavacamten versus 12.5% placebo) may have introduced bias in favour of mavacamten as a greater proportion of patients in the placebo group were not receiving any background therapy. The baseline and demographic characteristics of the VALOR-HCM trial appeared to be generally balanced between the treatment groups. Treatment discontinuation and study discontinuation among patients was low in both pivotal trials. The clinical expert consulted for this review indicated that the primary efficacy outcome of the EXPLORER-HCM trial, pVO_2 and NYHA functional class, are appropriate measures of functional capacity and symptom severity, respectively, in the indicated population. In both pivotal trials, HRQoL was measured using KCCQ-23 CSS scores as a key secondary outcome. The clinical expert consulted indicated that such tools are not typically used in clinical practice but are used in multiple studies. Disease-related symptoms were assessed using the newly developed HCMSQ instrument with the HCMSQ SoB domain assessed as a key secondary outcome in the EXPLORER-HCM trial. It should be noted that as approximately 28% of patients did not have KCCQ-23 CSS or HCMSQ SoB data collected at baseline or at their week 30 visit in the EXPLORER-HCM study, there is a risk of bias as those who completed the questionnaires may be fundamentally different than those who did not (i.e., differences in treatment response). However, for all imputation scenarios, ad-hoc sensitivity analyses were generally supportive of the findings of the primary analyses.

The VALOR-HCM trial is evaluating the use of mavacamten to reduce the need for SRT in patients who are guideline eligible and willing to participate in invasive therapies. As such, there is no direct evidence of mavacamten compared to SRT available for this review. There is also limited direct evidence comparing

mavacamten to disopyramide. Patients taking disopyramide were excluded from the EXPLORER-HCM trial and less than 20% of enrolled patients (n = 22) used disopyramide at baseline as monotherapy or in combination with BB and/or CCBs in the VALOR-HCM study. Subgroup analyses based on disopyramide use at baseline was not available for the VALOR-HCM trial, as statistical comparisons were not performed when the sample size within a subgroup was less than 20% of the overall population. Therefore, the comparative effectiveness of disopyramide versus mavacamten in this patient population is unknown. In terms of subgroups of interest, both pivotal trials included subgroup analyses by baseline background therapy (BB or CCB use) and the EXPLORER-HCM trial also examined NYHA class (II versus III) as a prespecified subgroup. For the primary end point in the EXPLORER-HCM trial, there was no statistically significant difference for the subgroup of patients taking BBs. However, all key secondary end points in the EXPLORER-HCM trial showed benefit for mavacamten compared with placebo across the evaluated subgroups, irrespective of BB use. The subgroup analyses may not have been powered to detect a treatment difference and there were no adjustments made for multiplicity. As such, all subgroup analyses are exploratory in nature. It should be noted that there was no clinical study report or statistical analysis plan available for the VALOR-HCM trial at the time of this review, which prevented CADTH from being able to fully appraise the potential for bias within the trial.

Compared to the Canadian population, the racial diversity in the pivotal trials was limited as most patients were white. In addition, no patients were recruited from Canada in either of the pivotal trials. However, the clinical expert noted that the lack of representation of patients from Canada does not reduce the generalizability of the results to Canadian clinical practice. While mavacamten has been approved by Health Canada for use in adult patients with symptomatic oHCM of NYHA functional class II to III, the VALOR-HCM trial included an unknown number of NYHA functional class IV patients. The VALOR-HCM trial is an ongoing randomized controlled trial evaluating the use of mavacamten to reduce the need for SRT in patients who are guideline eligible for invasive therapies with descriptive data available through to week 32. As such, it is uncertain if, in the long term, mavacamten can reduce the need for SRT among patients with oHCM who are symptomatic.

Indirect Comparisons

No indirect evidence was available.

Other Relevant Evidence

Additional descriptive efficacy and safety data for the VALOR-HCM trial through to week 32 and data from 1 open-label extension study (MAVA-LTE) were summarized in this report.

Description of Studies

An additional study report was published for the VALOR-HCM trial examining data up to week 32 among patients initially randomized to mavacamten (32 weeks of drug exposure) and for patients initially randomized to placebo who crossed over to mavacamten at week 16 (16 weeks of drug exposure). A total of 4 patients in the placebo group who elected to undergo SRT treatment or withdrew from the study during the first 16 weeks were not included in this analysis.

MAVA-LTE is an ongoing, dose-blinded, 5-year extension study to assess the long-term efficacy and safety of mavacamten; it is following patients who completed the EXPLORER-HCM trial through to week 38 (the EXPLORER-LTE cohort) and MAVERICK-HCM (a phase II trial in patients with nonobstructive HCM has not been assessed in this report). A total of 224 patients who enrolled in the EXPLORER-LTE trial cohort started mavacamten treatment at 5 mg once daily, regardless of their treatment group in the EXPLORER-HCM pivotal trial. Dose adjustments at week 4, week 8, and week 12 were based on site-read echocardiograms of Valsalva LVOT gradient and LVEF. At long-term extension (LTE) baseline, a total of 5.8% of patients in the EXPLORER-LTE trial cohort were classified as NYHA functional class I, 65.2% were classified as NYHA functional class II, 29.0% were classified as NYHA functional class III, and none were classified as NYHA functional class IV.

Efficacy Results

In the VALOR-HCM trial, at week 32, 1 or fewer NYHA class improvements was observed in 48 out of 53 (90.6%) patients in the original mavacamten group and 35 out of 50 (70%) patients in the crossover group. In the original mavacamten group, the mean change from baseline to week 32 in KCCQ-23 CSS score was 13.1 points (95% CI, 9.2 to 17.1), while in the placebo crossover group, the mean change in KCCQ-23 CSS score from week 16 to week 32 was 8.0 points (95% CI, 3.2 to 12.8). At week 32, 6 (10.7%) patients in the original mavacamten group and 7 (13.5%) patients in the placebo crossover group continued to meet the guideline criteria for SRT or elected to undergo the procedure. In the original mavacamten group, there was a reduction in resting, Valsalva, and postexercise LVOT gradients from baseline to week 32. A similar reduction in LVOT gradients in the crossover group was seen after 16 weeks of mavacamten exposure.

Among patients in the EXPLORER-LTE cohort, from LTE baseline to week 48 of the extension study, 35 (71.4%) patients had an improvement of 1 or more NYHA classes [redacted] Reductions from LTE study baseline were observed in both resting and Valsalva LVOT gradients with mavacamten treatment as assessed by both site- and central-readings in the extension study. However, the number of patients was relatively small during the end time points, making it difficult to draw any conclusion about the effects of mavacamten on LVOT gradients. [redacted] In line with the EXPLORER-HCM pivotal trial, NT-proBNP concentrations decreased at LTE week 4 and decreases were sustained over time to LTE week 72.

Harms Results

In the VALOR-HCM trial, through to week 32, the rate of SAEs was similar between the original mavacamten group and the placebo crossover group. There were no reported deaths, myocardial infarctions, or strokes in either group. Through to week 32, 9 patients, comprising 7 (12.5%) patients in the original mavacamten group and 2 (3.8%) patients in the placebo crossover group, required a temporary drug discontinuation due to an LVEF of lower than 50%. One patient in the placebo crossover group had a reduction of LVEF of 30% or less at week 31 associated with paroxysmal atrial fibrillation and heart failure. Following permanent mavacamten discontinuation, there was recovery and normalization of LVEF.

Among patients in the EXPLORER-LTE cohort, 62.9% of patients experienced at least 1 AE. The most common AEs (frequency ≥ 3%) were atrial fibrillation, [redacted] fatigue, nasopharyngitis, dizziness, headache,

dyspnea, and pain in extremity. One death, due to bacterial endocarditis, occurred in the EXPLORER-LTE cohort, which was deemed by the investigator to be unrelated to mavacamten. The most common SAEs among patients were cardiac failure (1.3%), pneumonia (0.9%), and atrial fibrillation (0.9%). A total of 2 (0.9%) patients permanently discontinued treatment due to AEs, with 1 patient discontinuing due to worsening of systemic lupus erythematosus, and 1 patient due to cardiac failure. No patients met the permanent discontinuation criteria of an LVEF of lower than 30%. A total of 11 (4.9%) patients demonstrated a total of 13 qualifying events meeting the criteria for a temporary treatment discontinuation, 4 (1.8%) of whom experienced an LVEF of lower than 50%.

Critical Appraisal

Results at week 32 of the VALOR-HCM trial provided additional data on the safety and efficacy of mavacamten. As all patients receiving placebo crossed over to mavacamten treatment at week 16, there was no active comparator, and all outcomes were descriptive in nature, making it difficult to make causal conclusions of the findings. Once patients receiving placebo crossed over to active treatment at week 16, investigators and patients were aware that all patients were receiving active treatment; thus, their expectations of treatment could affect reporting of subjective outcomes such as NYHA class, HRQoL, and adverse effects.

Among patients in the EXPLORER-LTE trial cohort, the baseline and demographic characteristics were similar to those seen in the pivotal trial. Treatment discontinuation and study discontinuation among patients were low in the extension study, as observed in both pivotal trials. pVO_2 from the pivotal trial was not assessed in the extension study, and secondary and exploratory outcomes like HCMSQ and EQ-5D-5L data were collected in the extension study but will not be assessed until the final analysis is conducted. The absence of these parameters in the interim analysis makes it difficult to interpret the efficacy results of mavacamten for the extension study. [redacted], the number of patients at later time points in all efficacy analyses were relatively few at the time of the data cut; therefore, these results need to be interpreted with caution. The generalizability of the efficacy and harms outcomes and the lack of racial diversity mentioned in the main studies are applicable to the extension study.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with symptomatic oHCM of NYHA class II to III
Treatment	Mavacamten plus a BB or CCB
Dose regimen	5 mg once daily, with dose adjustments recommended based on LVOT gradient
Submitted price	Mavacamten 2.5 mg, 5 mg, 10 mg, and 15 mg: $61.6000 per capsule

Component	Description
Treatment cost	$22,484 per year
Comparator	BBs or CCBs (73% of patients assumed to receive BBs [53% metoprolol and 47% bisoprolol] and 23% assumed to receive CCBs [50% diltiazem and 50% verapamil])
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (41 years)
Key data source	EXPLORER-HCM trial
Key limitations	• The full Health Canada population was not modelled. Effectiveness of mavacamten plus a BB or CCB in the pharmacoeconomic model was based on observations from the EXPLORER-HCM trial, in which most patients received mavacamten as second-line therapy. The cost-effectiveness of mavacamten as first- or third-line therapy is unknown. • Disopyramide was not included as a comparator, which was deemed inappropriate based on clinical practice guidelines and the clinical expert feedback obtained by CADTH for this review. • The survival benefit predicted by the sponsor's submitted model for mavacamten plus a BB or CCB compared to BBs or CCBs is highly uncertain and has not been shown in clinical trials. • Several assumptions related to subsequent therapy are highly uncertain and not aligned with expected clinical practice. As a result of these assumptions, the sponsor's model predicts that more patients will undergo septal reduction therapy after mavacamten compared to with BBs or CCBs, which is contradictory to the findings of the VALOR trial. • The sponsor's use of a shorter observation period for the efficacy of mavacamten plus a BB or CCB compared with BBs or CCBs biases the results in favour of mavacamten. • The relative long-term effectiveness of mavacamten compared to BBs or CCBs is highly uncertain. • The sponsor incorporated response-based stopping rules for mavacamten, which are not recommended in the product monograph or implemented in the pivotal trials. The clinical expert consulted by CADTH indicated that criteria adopted by the sponsor in the model are not aligned with how mavacamten is expected to be used in clinical practice.
CADTH reanalysis results	• In CADTH reanalyses, CADTH removed the survival benefit for mavacamten, adopted alternative assumption on subsequent treatment among patients receiving BBs or CCBs, adopted the same observation period to determine the efficacy of mavacamten and a BB or CCB, and removed the response-based stopping rules for mavacamten. CADTH was unable to address the omission of disopyramide as a comparator. • Results of the CADTH reanalyses, suggest that mavacamten plus a BB or CCB is more costly (incremental costs = $264,737) and more effective (incremental QALYs = 0.46) than BBs or CCBs alone, resulting in an ICER of $576,295 per QALY gained when used in the second-line setting for patients with baseline NYHA class II or III. A price reduction of 73% for mavacamten would be required for mavacamten plus a BB or CCB to be considered cost-effective compared to BBs or CCBs at a willingness-to-pay threshold of $50,000 per QALY. • The cost-effectiveness of mavacamten compared to disopyramide is unknown. Furthermore, the results were sensitive to the assumptions about the long-term relative effectiveness of mavacamten. The CADTH reanalysis estimated a smaller benefit in the extrapolated period compared to the sponsor, although uncertainty remains regarding the expected magnitude of the clinical benefit. If treatment effectiveness waning occurs, a higher price reduction would be required.

BB = beta-blocker; CCB = calcium channel blocker; ICER = incremental cost-effectiveness ratio; LVOT = left ventricular outflow tract; LY = life-year; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The number of patients eligible for mavacamten plus a BB or CCB is highly uncertain. The sponsor's method of deriving the eligible population size may have double counted the proportion of patients who are diagnosed, thus underestimating the number eligible. Most of the epidemiological parameters used by the sponsor were based on expert opinion or data that could not be validated by CADTH.
- In some settings, the uptake of mavacamten may be higher than estimated by the sponsor.

CADTH reanalyses included removing the double counting of symptomatic patients by assuming that all patients diagnosed with oHCM are symptomatic and including mark-ups and dispensing fees. CADTH reanalyses suggest that the overall budget impact to the public drug plans of introducing mavacamten for the treatment of symptomatic oHCM in adult patients is $54,641,769 over 3 years (year 1 = $4,807,445; year 2 = $13,723,972; year 3 = $36,110,351).

The estimated budget impact is sensitive to assumptions about the number of patients eligible for mavacamten and the rate of uptake of mavacamten. Should the number of patients eligible to receive mavacamten increase or the rate of uptake of mavacamten among eligible patients increase, the budget impact of reimbursing mavacamten will be higher than the CADTH base case.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: February 23, 2023

Regrets: Three of the expert committee members did not attend.

Conflicts of interest: None