REPORT AT A GLANCE: HYPERTROPHIC CARDIOMYOPATHY

NOVEMBER 2021

KEY FINDINGS

	mavacamten (MyoKardia and Bristol-Myers Squibb)
Evidence Rating	P/I; promising but inconclusive to determine if mavacamten added to first-line therapy provides a net health benefit over first-line therapy care alone or the addition of disopyramide.
Estimated Annual Price	Placeholder price: $75,000
Annual Health-Benefit Price Benchmark	$12,000-$15,000
Change from Annual Price Required to Reach Threshold Price	N/A: discounts not presented due to placeholder price

"Hypertrophic cardiomyopathy is a genetic disorder of the heart muscle that can cause shortness of breath and chest pain, and also arrhythmias that can result in strokes or even sudden death. The evidence suggests that mavacamten may deliver important health benefits for patients with a lower rate of side effects than seen with some other medications for HCM, but clinical experts differ in their opinions about the long-term clinical implications of mavacamten reducing left ventricular ejection fraction in some patients. Additional safety data are needed to resolve these issues."

– ICER's Chief Medical Officer, David Rind, MD

THEMES AND RECOMMENDATIONS

- All stakeholders have a responsibility to facilitate meaningful patient access to multidisciplinary centers of excellence for HCM in ways that do not exacerbate disparities.
- The manufacturer of mavacamten should commit to sponsoring research that will address the lack of data on the comparative effectiveness of mavacamten versus disopyramide and septal reduction procedures.
- The manufacturer of mavacamten should align the price of mavacamten with the explicit and transparent estimates of its treatment benefits for patients and families. Pricing should also be moderated to reflect the uncertainty about longer-term safety until such time as further outcomes data are generated.
- Payers should use the FDA label as the guide to coverage policy and engage clinical experts and diverse patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Hypertrophic cardiomyopathy (HCM) is a genetic disorder involving sarcomeres in heart muscle that can cause symptoms such as chest discomfort and shortness of breath, particularly with exertion. Apart from managing symptoms, key components of therapy include placement of implanted cardioverter defibrillators (ICDs) for patients at high risk of sudden death and anticoagulation for patients who have both HCM and atrial fibrillation.

For patients with a specific subtype of HCM, hypertrophic obstructive cardiomyopathy (HOCM), obstruction of the left ventricular outflow tract (LVOT) can be an important contributor to exertional symptoms. The LVOT is the conduit through which blood exits the heart to the rest of the body. While LVOT obstruction is one important target for therapy to reduce symptoms, there are other causes of symptoms including diastolic dysfunction, microvascular angina (obstruction of small heart artery vessels), and irregular heart rhythms.

For HOCM patients with shortness of breath related to LVOT obstruction, medications can improve symptoms. Beta blockers and calcium channel blockers reduce the forcefulness of the heart's contraction, reducing the LVOT gradient, thus improving symptoms. However, beta blockers and calcium channel blockers have important side effects, including fatigue that can interfere with work or daily activities, dizziness, and sexual dysfunction.

When these first-line therapies are insufficient or not well tolerated, second-line treatment options include adding disopyramide or performing septal reduction procedures. Disopyramide has important side effects as well, and drug shortages limit access to the long-acting version. Septal reduction procedures include surgical myectomy (a type of open-heart surgery) or alcohol septal ablation, a controlled heart attack that reduces the thickness of the heart muscle causing LVOT obstruction. Those procedures can have substantial benefit, but they have a low but meaningful risk of death. Furthermore, clinical outcomes following these procedures may be worse outside centers of excellence. As such, there is substantial unmet need for the management of exertional symptoms in patients with symptomatic HOCM, particularly among patients that do not have good access to specialized centers.

A novel agent, mavacamten, has been tested in clinical trials. Mavacamten reduces adenosine triphosphatase activity in cardiac myosin heavy chain, one of the proteins in heart muscle cells, and thus reduces the contraction of the heart that can contribute to obstruction. A United States (US) Food and Drug Administration (FDA) decision on approval of mavacamten is expected in early 2022. This report examines the comparative effectiveness and cost effectiveness of mavacamten in patients with symptomatic HOCM.

The key trial in such patients is EXPLORER, a Phase III randomized trial comparing mavacamten to placebo in 251 patients receiving first-line treatments. Mavacamten was more effective than placebo at meeting a primary clinicians composite endpoint of 1.5 mL/kg per min or greater increase in peak oxygen consumption (pVO2) and at least one New York Heart Association (NYHA) class reduction or a 3.0 mL/kg per min or greater pVO2 increase without NYHA class worsening (37% vs. 17%, p=0.0005). Among patients who completed the Kansas City Cardiomyopathy Questionnaire (KCCQ), the KCCQ overall summary score was more improved among patients assigned to mavacamten than placebo (+14.9 vs. +5.4, p<0.0001). Serious adverse events were uncommon in EXPLORER and similar between arms of the trial. Some clinical experts noted conceptual concerns about reductions in ejection fraction and myocardial thickness with mavacamten: these changes can be beneficial but

Clinical Analyses

could result in long-term harm if they persist or recover then worsen over time. Other clinical experts are much less concerned about this potential harm. In the absence of additional long-term evidence on mavacamten, we need to consider the potential for possible net harms, and we rate mavacamten in addition to usual care compared with usual care alone as promising but inconclusive ("P/I").

When comparing mavacamten with disopyramide, we are limited by the absence of head-to-head randomized trials and the absence of randomized trials of disopyramide. Disopyramide has known side effects and contraindications. Furthermore, data supporting use of disopyramide are relatively weak and potentially exaggerate the true treatment effect due to study design. On balance, we consider the evidence for mavacamten compared with disopyramide to be promising but inconclusive ("P/I") as well.

We lack randomized trials of septal reduction therapies either to each other, compared with no procedure, or compared with mavacamten. Observational data appear to show greater improvements in functional outcomes with such procedures than was seen in the EXPLORER trial, however, these procedures have a small risk of short-term serious adverse events including death. Overall, among patients who are eligible for a septal reduction procedure, net benefits are likely greater with a procedure than with mavacamten. However, we also believe the choice between a procedure with a short-term risk of death and mavacamten would be highly dependent on individual patient preferences. Given this, we are not assigning an evidence rating to this comparison: such decisions will need to be made on a case-by-case basis through discussions among patients, families, and clinicians.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

We created a semi-Markov model to estimate discounted lifetime time horizon costs, quality-adjusted life years (QALYs), life years, years in NYHA class I, and equal value of life years (evLYs) for mavacamten along with standard first-line therapies and several comparators. Table 1 presents the base-case cost-effectiveness results.

Mavacamten used along with standard first-line treatment was projected to generate higher amounts of QALYs than standard first-line treatment alone. However, at the placeholder cost of $75,000, the incremental cost-effectiveness ratio was well above standard thresholds ($1,200,000 per QALY). When compared with disopyramide, the incremental cost per QALY was even higher, and mavacamten was found to be dominated by both myectomy and septal ablation. From the cost-effectiveness analysis, we estimated the health benefit price benchmark (HBPB) for mavacamten to be $12,000 to $15,000 annually. The actual cost effectiveness of mavacamten will depend on its price.

Potential other benefits of mavacamten include more access to treatment options because septal reduction procedures are mainly available at specialized centers. When septal reduction procedures are performed at lower-volume centers, outcomes are worse although these differences could reflect both differences in quality and/or unmeasured confounding. There have also been national shortages of the long-acting form of disopyramide. In part based on the shortage as

Economic Analyses

well as other issues including side effects and limited efficacy, few patients are actually taking disopyramide. However, some patients and patient groups emphasized that disopyramide is still an important treatment option. Finally, mavacamten will be a new option available for patients at points in their lives when they are making important life choices regarding education, work, and raising families, which could provide benefits over and above the improvement in QALYs calculated in the model.

Table 1. Incremental Cost-Effectiveness Ratios for Mavacamten* in the Base Case

Intervention (Trial)	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Additional NYHA I Year
Mavacamten	Standard treatment	$1,200,000	Undefined	$1,200,000	$219,000
	Disopyramide	$1,500,000	Undefined	$1,500,000	$278,000
	Myectomy	Dominated	$5,600,000	N/A†	Dominated
	Septal ablation	Dominated	$7,000,000	N/A†	Dominated

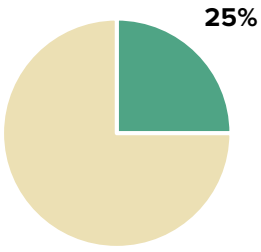
evLY: equal value of life years, N/A: not applicable, NYHA: New York Heart Association, QALY: quality-adjusted life year

*Price assumed for mavacamten was a placeholder of $75,000 per year.

†Incremental cost per evLY gained not applicable due to fewer lifetime QALYs for mavacamten as compared to myectomy and septal ablation.

POTENTIAL BUDGET IMPACT

Assuming the placeholder price of $75,000 per year, only 25% of the eligible patients could be treated within five years (assuming 20% uptake each year), before crossing the ICER potential budget impact threshold of $734 million per year. All eligible patients could be treated within five years without crossing the ICER potential budget impact threshold at the price to reach either $50,000/QALY, $100,000/QALY, or $150,000/QALY.



mavacamten

Percent of eligible patients with HCM that could be treated in a given year before crossing the ICER potential budget impact threshold

Public Meeting Deliberations

VOTING RESULTS

- A majority of panelists found that the evidence is not adequate to demonstrate a net health benefit of mavacamten added to background therapy when compared to background therapy alone.

- A majority of panelists found that the evidence is not adequate to demonstrate a net health benefit of mavacamten when compared to disopyramide.

During their deliberations, panel members also weighed the therapies' other potential benefits, disadvantages, and contextual considerations. For both treatments, voting highlighted the following as particularly important for payers and other policymakers to note:

- The magnitude of the lifetime impact on individuals living with HCM as an important contextual consideration for any effective therapy for HCM;

- The effect of mavacamten on patients' ability to achieve major life goals related to education, work, or family life;

- The effect of mavacamten on caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

- Opportunities to improve access to treatment with an oral therapy that does not require access to a center with expertise in myectomy or septal ablation; and

- Availability of a treatment with different timing and types of risks and benefits , relative to existing procedural and surgical optionsreflecting that, while mavacamten does not improve symptoms as much as septal procedures, it also does not carry an immediate short-term risk of death or the need for recovery from a procedure.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

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