Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR044.0625	**CARDIOVASCULAR AGENTS** **CAMZYOS®** (mavacamten capsule)
Effective Date: 8/1/2025	**Review/Revised Date**: 04/23, 04/24, 08/24, 042/5 (MTW)
Original Effective Date: 10/22	**P&T Committee Meeting Date**: 08/22, 06/23, 06/24, 10/24, 06/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications not otherwise excluded from the benefit

REQUIRED MEDICAL INFORMATION:
Initial authorization requires documentation of all the following:

1. Diagnosis of hypertrophic cardiomyopathy (HCM), defined as left ventricular hypertrophy (LVH) in the absence of another cardiac, systemic, or metabolic disease capable of producing the magnitude of hypertrophy evident, and one of the following:
    a. Left ventricle wall thickness of 15 mm or greater **OR**
    b. Left ventricle wall thickness of 13 mm or greater with family history of HCM or in conjunction with a positive genetic test
2. New York Heart Association (NYHA) class II, III, or IV
3. Left ventricular ejection fraction (LVEF) 55% of greater
4. Left ventricular outflow tract (LVOT) peak gradient 50 mmHg or greater at rest or with provocation
5. Documented trial and failure of one of the following (titrated to the maximum tolerated dose), unless both are not tolerated or contraindicated:
    a. A formulary generic non vasodilating beta blocker (such as propranolol, metoprolol, atenolol, bisoprolol)
    b. A formulary generic nondihydropyridine calcium channel blocker (verapamil or diltiazem)

Reauthorization requires documentation of both of the following:
1. A positive clinical response, as evidenced by at least one of the following:
    a. Improvement in symptoms (such as dyspnea, fatigue, chest pain, palpitations, dizziness, fainting) OR
    b. NYHA class reduction
2. Patient has a left ventricular ejection fraction (LVEF) of greater than or equal to 50%

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
May be approved for patients aged 18 years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a cardiologist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for one year.

QUANTITY LIMIT:
30 capsules per 30 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Mavacamten is an allosteric and reversible inhibitor selective for cardiac myosin ATPase, designed to reduce actin-myosin cross-bridge formation. This results in

reduced cardiac contractility, reduced dynamic LVOT obstruction, and improved cardiac filling pressures.

- The recommended starting dose is 5 mg orally once daily without regard to food. Recommended doses following titration are 2.5 mg, 5 mg, 10 mg, or 15 mg once daily.
- Because of the observed decrease in LVEF <50% in 7% to 10% of patients in clinical trials, mavacamten is only available through a restricted program called the Camzyos REMS Program.
- According to the package insert, initiation in patients with LEVF <55% is not recommended, and therapy should be stopped if LVEF <50% or if the patient experiences worsening clinical status

FDA APPROVED INDICATIONS:

The treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms.

POSITION STATEMENT:

- HCM is the most common genetic heart disease in the United States, with an estimated prevalence of one in every 200 to 500 people[6]. About 2/3 of these patients have obstructive HCM, characterized by unexplained left ventricular (LV) hypertrophy associated with dynamic LV outflow tract obstruction. Diagnosis is most common in people aged 40 years and older. Symptoms can include chest discomfort, shortness of breath, palpitations, dizziness, and syncope. While many patients are asymptomatic, all patients are at risk of sudden cardiac death.
- The 2020 AHA/ACC HCM guideline characterizes HCM as left ventricular hypertrophy (LVH) “in the absence of another cardiac, systemic, or metabolic disease capable of producing the magnitude of hypertrophy evident in a given patient and for which a disease-causing sarcomere (or sarcomere-related) variant is identified, or genetic etiology remains unresolved”[6]. Examples of other causes of LVH include hypertension, aortic valve stenosis, ventricular septal defects, and intense athletic training.
- Diagnosis of HCM is defined as unexplained left ventricular hypertrophy with maximal left ventricular wall thickness (from anywhere in the left ventricle wall) of ≥15 mm, or ≥13 mm if familial hypertrophic cardiomyopathy. The most common genetic mutations causing HCM are: MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, TNNC1, ACTN2, MYOZ2, and ACTC1 gene variants[11]. Out of these, 50% are MYH7 and MYBPC3 gene variants. Obstruction is evident with a peak left ventricular outflow tract (LVOT) gradient of ≥30 mmHg, with resting or provoked gradients ≥50 mmHg generally considered to be the threshold for septal reduction therapy (SRT) in those patients with drug-refractory symptoms[6]. LVOT obstruction is dynamic and variable and can change in response to

decreased preload, lower afterload, daily activities, and food and alcohol intake. Maneuvers may be required in patients with low or absent peak resting gradients to demonstrate the presence of LVOT obstruction.

- Guidelines for the management of HCM include the AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines and the 2023 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. Treatment recommendations target symptom relief and prevention of sudden cardiac death; there are no pharmacologic therapies with evidence of altering the natural history of HCM.
    - Non vasodilating beta-blockers are generally considered first-line therapy[6,13]. Beta blockers improve symptoms of obstruction, angina, dyspnea, and reduce the risk of ventricular arrhythmias, and are useful in patients both with and without outflow obstruction[11]. Beta blockers should be titrated to a dose where the patient experiences symptom benefit and treatment should not be considered a failure unless physiologic evidence of beta-blockade occurs, such as suppression of resting heart rate. Non-dihydropyridine calcium channel blockers (verapamil and diltiazem) are reasonable alternatives to beta blockers and are used similarly, to reduce cardiac chronotropy and inotropy, leading to improved diastolic filling, reduced outflow gradient, and improved perfusion of the sub-endocardium[11]. Caution is advised in using them in patients with either severe outflow obstruction (because of their vasodilatory effect in the peripheral vasculature) or severe heart failure in non-obstructive disease (because of negative inotropy).
    - The 2023 ESC Guidelines for the management of cardiomyopathies have been updated to include recommendations regarding mavacamten. The guideline notes that without head-to-head comparisons, mavacamten should not be used as first-line therapy, however evidence is sufficient to support its use as a second-line therapy when optimal medical therapy with beta-blockers, calcium channel blockers, and/or disopyramide is ineffective or not tolerated. Mavacamten should not be used with disopyramide but can be used in combination with beta-blockers or calcium channel blockers.
    - In the updated 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline, it is recommended that patients with obstructive HCM on beta blockers or nondihydropyridine calcium channel blockers who continue to have symptoms attributable to LVOTO add on therapy with a myosin inhibitor (adult patients only), disopyramide (in combination with an atrioventricular nodal blocking agent), or undergo SRT performed at experienced centers.

- Disopyramide has been shown to improve symptoms and reduce outflow gradients in patients with obstructive HCM who have failed first line therapy and is particularly important in patients who are not candidates for SRTs[6]. Side effects can be more significant than with beta-blockers or non-dihydropyridine calcium channel blockers and include risk of QTc prolongation and anticholinergic side effects. Routine ECG monitoring is required. Despite this, disopyramide remains a reasonable pharmacologic option for patients who remain symptomatic with high outflow gradients and for patients who remain symptomatic with beta-blockers and/or calcium channel blockers[11]. There is no known role for disopyramide in HCM patients without an obstructive gradient.
- Septal reduction therapy (SRT: septal myectomy, septal ablation) is generally used in patients with obstructive HCM who remain severely symptomatic (NYHA functional class III or IV) and/or have recurrent exertional syncope despite optimate medical therapy in order to relieve left ventricular outflow tract obstruction (LVOTO), and potentially improve survival[6,7]. SRT is rarely indicated for asymptomatic patients, and there is insufficient evidence to recommend SRT to improve patient survival as the sole indication for the procedures[6]. The 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline notes that SRT is very effective at relieving LVOTO and can be used as second-line therapy instead of mavacamten or disopyramide.

- The efficacy for mavacamten was established in two phase 2, double-blind, placebo-controlled clinical trials. In the EXPLORER-HCM (NCT03470545)[9] trial, adults (N=251) with HCM with a left ventricular outflow tract (LVOT) gradient of ≥ 50 mmHg, NYHA class II-III symptoms, and left ventricular ejection fraction (LVEF) ≥ 55% were included. The primary endpoint was a clinical response, defined as either a 1.5 mL/kg per min or greater increase in pVO2 and at least one NYHA class reduction OR a 3.0 mL/kg per min or greater improvement in pVO2 and no worsening of NYHA class. 33% of mavacamten patients achieved a clinical response, compared to 11% in the placebo group. 27% of patients on mavacamten had a complete response (compared with 1% in the placebo group, defined as an LVOT gradient reduction to <30 mmHg and improvement to NYHA class I. Mavacamten was well tolerated and has a good safety profile; a small subset of patients developed transient LV systolic dysfunction, which resolved after temporary discontinuation of the drug. In the VALOR-HCM (NCT04349072)[12] (N=112) trial, adult patients with obstructive HCM referred for septal reduction therapy (SRT) due to intractable symptoms showed that mavacamten significantly reduced the proportion of patients meeting criteria for SRT at 16 and 32 weeks. Small CMR and ECHO substudies suggest that mavacamten may

also lead to positive myocardial remodeling, with reduction in myocardial mass, LV wall thickness, and left atrial volume.

- The Institute for Clinical and Economic Review (ICER) conducted a review of mavacamten for Hypertrophic Cardiomyopathy in November 2021. Summary of conclusions:
    - In the absence of additional long-term evidence, ICER considers the potential for possible net harms, and rates mavacamten promising but inconclusive when added to usual care versus usual care alone. Due to a lack of head-to-head randomized trials and the absence of randomized trials of disopyramide, the evidence compared with disopyramide was also determined to be promising but inconclusive. Based on data from observational studies, ICER predicts that net benefits are likely greater with SRT than with mavacamten. Due to the small but significant adverse outcomes with SRT, including death, the choice between a procedure and mavacamten should be made on a case-by-case basis among patients, families, and clinicians.
    - The annual health-benefit price benchmark (HBPB) for mavacamten was estimated to be $12,000-$15,000. With an estimated annual WAC of $89,500, the incremental cost-effectiveness ratio is well above standard thresholds (most recently estimated to be $84,000 per quality-adjusted life year [QALY]), as compared to standard treatment or disopyramide ($1,200,000 and 1,500,000 per QALY, respectively).

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