Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

CAMZYOS 2.5 mg hard capsules
CAMZYOS 5 mg hard capsules
CAMZYOS 10 mg hard capsules
CAMZYOS 15 mg hard capsules

mavacamten

PLGB 15105/0180 - 0183

BRISTOL-MYERS SQUIBB PHARMA EEIG

LAY SUMMARY

Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules
mavacamten

This is a summary of the Public Assessment Report (PAR) for Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Camzyos in this lay summary for ease of reading.

These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 26 June 2023 (EMEA/H/C/005457/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

These applications were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

For practical information about using Camzyos, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules and what are they used for?

Camzyos is used to treat adults with a type of heart disease called obstructive hypertrophic cardiomyopathy (oHCM).

Hypertrophic cardiomyopathy (HCM) is a condition where the walls of the left heart chamber (ventricle) contract harder and become thicker than normal. As the walls thicken they can block (obstruct) the flow of blood out of the heart and can also make the heart stiff. This obstruction makes it more difficult for blood to flow into and out of the heart and be pumped to the body with each heartbeat, a condition known as obstructive hypertrophic cardiomyopathy (oHCM).

Symptoms of oHCM are chest pain and shortness of breath (especially with physical exercise); tiredness, abnormal heart rhythms, dizziness, feeling about to faint, fainting (syncope) and swelling of the ankles, feet, legs, abdomen and/or veins in the neck.

How do Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules work?

Camzyos works by reducing excess contraction of the heart and the obstruction to blood flow to the body. As a result, it may improve patient’s symptoms and ability to be active.

How are Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules used?

The pharmaceutical form of Camzyos is hard capsules and the route of administration is oral (by mouth). The capsules should be swallowed whole with a glass of water at about the same time each day. The medicine can be taken with food or between meals.

The recommended starting dose is 2.5 mg or 5 mg taken by mouth once daily. The patient’s doctor may do a test to check how this medicine is broken down (metabolised) in the

patient's body. The result may guide the Camzyos treatment. If the patient has liver problems, their doctor may also prescribe a reduced starting dose.

The patient's doctor will monitor how well their heart is working whilst they take Camzyos using echocardiograms and may change the dose (increase, lower, or temporarily stop) based on the results.

The patient's doctor will let them how much Camzyos to take and will prescribe a single daily dose of either 2.5 mg, 5 mg, 10 mg or 15mg. The maximum dose is 15 mg once daily. Patients must only take one capsule each day for the dose the doctor has prescribed to ensure that they receive the correct amount of Camzyos. The patient should always take the medicine exactly as their doctor has told them. The patient should check with their doctor if they are not sure.

The first echocardiogram will be done before a patient starts treatment, and then again during follow-up visits at week 4, 8 and 12 to assess their response to Camzyos. Routine echocardiograms will then be done every 12 weeks. If the doctor changes the dose of Camzyos at any point, an echocardiogram will be done 4 weeks afterwards to make sure the dose the patient is receiving is beneficial.

After the starting dose and monitoring, the patient's doctor will prescribe the patient a single daily dose of either 2.5 mg, 5 mg, 10 mg or 15 mg.

For further information on how Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

What benefits of Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules have been shown in studies?

The effectiveness of Camzyos was compared with placebo (a dummy treatment) in two main studies. The main measure of effectiveness in the first study, involving 251 patients with oHCM, was the proportion of patients who achieved a pre-defined level of improvement in exercise capacity (measured by the maximum volume of oxygen used during exercise) together with an improvement or stabilisation in symptoms of the disease. After 30 weeks of treatment, 37% of patients treated with Camzyos achieved this improvement compared with 17% of those treated with placebo.

The second study involved 112 patients with oHCM who were eligible for septal reduction therapy (SRT), where the size of the thickened heart muscle is reduced through surgery or a procedure using a catheter (a thin tube passed through an artery into the heart). After 16 weeks of treatment with Camzyos, 18% of patients proceeded with SRT or were still eligible for SRT compared with 77% of those who received placebo.

What are the possible side effects of Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules?

For the full list of all side effects reported with Camzyos, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine.

Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why were Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules approved?
The MHRA decided that the benefits are greater than the risks and recommended that these medicines can be approved for use.

What measures are being taken to ensure the safe and effective use of Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Camzyos. The RMP details the important risks of Camzyos, how these risks can be minimised, any uncertainties about Camzyos (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Camzyos:

Important identified risks	None
Important potential risks	Heart failure due to systolic dysfunction
	Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers
	Embryo-foetal toxicity
Missing information	Patients with Class IV NYHA
	Patients being treated with disopyramide
	Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)
	Long-term safety, including detrimental CV effects
	Use during lactation
	Safety in CYP2C19 poor metabolizers

The company responsible for Camzyos will provide risk minimisation materials to patients and to healthcare professionals. These include a patient card that will contain important safety information, including the need to avoid pregnancy during treatment, as well as instructions on when to contact the doctor if patients have new or worsening symptoms of heart failure. The patient card also contains information on the risk of interaction with other medicines. A checklist will also be provided to healthcare professionals regarding the risks associated with Camzyos.

The company that markets Camzyos will also conduct further studies in Europe, the US and Japan to provide further data on the safety and efficacy of Camzyos:

- Mavacamten Real-World Safety study (CV027013): a post-authorisation long-term observational study in Europe
- MYK-461-007/CV027003 (MAVA-LTE): a long-term safety extension study of mavacamten in adults with hypertrophic cardiomyopathy who have completed the studies MAVERICK-HCM (MYK-461-006) or EXPLORER-HCM (MYK-461-005)

- MYK-461-017/CV027006 (VALOR-HCM [LTFU]): A randomised, double-blind, placebo-controlled study to evaluate mavacamten in adults with symptomatic obstructive hypertrophic cardiomyopathy who are eligible for septal reduction therapy
- CV027012 (DISCOVER-HCM): deliver insights in hypertrophic cardiomyopathy and observational outcomes in real-world: US Prospective Registry Study
- CV027031 (ODYSSEY-HCM): A randomised, double-blind, placebo-controlled clinical study to evaluate mavacamten in adults with symptomatic non-obstructive hypertrophic cardiomyopathy
- CV027004 (HORIZON-HCM): a phase 3, open-label, single-arm, clinical study to evaluate efficacy, safety and tolerability of mavacamten in adults with symptomatic obstructive hypertrophic cardiomyopathy

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Camzyos are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

A RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules
Marketing authorisations were granted in Great Britain on 28 July 2023.

The full PAR for Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules follows this summary.

This summary was last updated in March 2024.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules (PLGB 15105/0180 - 0183) could be approved.

The products are approved for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

The active ingredient in Camzyos 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules is mavacamten. Mavacamten is a selective, allosteric, and reversible cardiac myosin inhibitor. Mavacamten modulates the number of myosin heads that can enter power-generating states, thus reducing (or in HCM normalizing) the probability of force-producing systolic and residual diastolic cross-bridge formation. Mavacamten also shifts the overall myosin population towards an energy-sparing, but recruitable, super-relaxed state. Excess cross-bridge formation and dysregulation of the super-relaxed state of myosin are mechanistic hallmarks of HCM, which can result in hyper-contractility, impaired relaxation, excess energy consumption, and myocardial wall stress. In HCM patients, cardiac myosin inhibition with mavacamten normalises contractility, reduces dynamic LVOT obstruction, and improves cardiac filling pressures.

These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 26 June 2023 (EMEA/H/C/005457/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

The applications were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

In line with the legal requirements for children's medicines, the applications included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) EMEA-002231-PIP01-17. At the time of the submission of the applications, the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations were granted on 28 July 2023.

II. PRODUCT INFORMATION

Summaries of Product Characteristics (SmPCs)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET
The PIL is in line with current guidelines and is satisfactory.

LABEL
The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS
The MHRA considered that the quality data submitted for these applications is satisfactory. The grant of marketing authorisations were recommended.

IV. NON-CLINICAL ASPECTS
The MHRA considered that the non-clinical data submitted for these applications is satisfactory. The grant of marketing authorisations were recommended.

V. CLINICAL ASPECTS
The MHRA considered that the clinical data submitted for these applications is satisfactory. The grant of marketing authorisations were recommended.

VI. RISK MANAGEMENT PLAN (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional risk minimisation measures have been proposed:

Heart failure due to systolic dysfunction	
Important potential risks	
Evidence for linking the risk to the medicine	Systolic dysfunction (reversible) has been reported in mavacamten clinical trials. Heart failure due to systolic dysfunction represents a clinical outcome of an exaggerated on-target effect (excessive decrease in myocardial contractility) of mavacamten that has been seen alone or in combination with intercurrent illnesses (eg, uncontrolled atrial fibrillation, serious infection, stress cardiomyopathy) in clinical trials. Systolic dysfunction has been reversible in the clinical program upon dose discontinuation and down titration. Excessive or prolonged reduction in ejection fraction can be life-threatening.
Risk factors and risk groups	History of significant ischemic events, history of arrhythmias, and history of systolic dysfunction are identified as prior risk factors for developing systolic dysfunction leading to heart failure. Intercurrent events of stress cardiomyopathy, atrial fibrillation, infection, arrhythmias with rapid ventricular rate, ischemia, and higher mavacamten concentrations may contribute to new events of systolic dysfunction or make it more difficult to control. Drug-drug interactions with CYP2C19 inhibitors or moderate or strong CYP3A4 inhibitors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: • HCP Checklist • Patient Card and Patient Guide

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (PASS; CV027013) • MAVA-LTE (MYK-461-007/CV027003) • VALOR-HCM (Long-term follow-up [LTFU]) (MYK-461-017/CV027006) • DISCOVER-HCM (CV027012)

Important potential risks

Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ulrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers	
Evidence for linking the risk to the medicine	Pharmacokinetic parameters from in vitro studies, population PK modeling and drug interaction studies in healthy volunteers, demonstrated metabolism largely by CYP2C19 and CYP3A4 and increased mavacamten concentrations in the presence of CYP2C19 and moderate or strong CYP3A4 inhibitors. In the pivotal EXPLORER study, 7 (6%) subjects in the mavacamten group and 2 (2%) subjects in the placebo group experienced reversible reductions in left ventricular ejection fraction (LVEF) to < 50% (median 48%: range 35-49%) while on treatment. Among 7 subjects in the mavacamten group with on-treatment LVEF reduction to < 50%, concentration levels were not highly correlated with the changes (eg, 4 of 7 events of LVEF < 50% occurred with mavacamten plasma concentrations < 700 ng/mL, and 3 of 7 occurred with mavacamten concentrations > 700 ng/mL). Therefore, elevation in plasma concentration did not consistently precede changes in LVEF. In all 7 patients treated with mavacamten, LVEF recovered following interruption of mavacamten and none of them were associated with an event of heart failure.
Risk factors and risk groups	Patients who may be receiving CYP2C19 or moderate or strong CYP3A4 inhibitors (prescription drugs, over the counter [OTC] medications, herbal products). CYP2C19 poor metabolizers may have increased mavacamten expsoures (up to 3 times) that can lead to an increased risk of systolic dysfunction compared to normal metabolizers.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.5 Additional risk minimisation measures: • HCP Checklist • Patient Card and Patient Guide
Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	Nonclinical developmental toxicity study findings were suggestive of a teratogenic potential of mavacamten at therapeutic exposures.
Risk factors and risk groups	Females of childbearing potential who are not using highly effective contraception.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4, 4.6, and 5.3 Additional risk minimisation measures: • HCP Checklist • Patient Card and Patient Guide

Missing information

Patients with Class IV NYHA	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.1 and 5.1
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (PASS; CV027013) • DISCOVER-HCM (CV027012)

Patients being treated with disopyramide	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 5.1
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (PASS; CV027013) • VALOR-HCM (LTFU) (MYK-461-017/CV027006) • DISCOVER-HCM (CV027012)

Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.5
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (PASS; CV027013) • VALOR-HCM (LTFU) (MYK-461-017/CV027006) • DISCOVER-HCM (CV027012)

Long-term safety, including detrimental CV effects	
Risk minimisation measures	Routine risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (PASS; CV027013) • MAVA-LTE (MYK-461-007/CV027003) • VALOR-HCM (LTFU) (MYK-461-017/CV027006) • DISCOVER-HCM (CV027012) • Planned meta-analysis to assess CV outcome safety

Use during lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 Additional risk minimisation measures:

	None
Safety in CYP2C19 poor metabolizers	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 4.5
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • HORIZON-HCM (CV027004) (oHCM) • ODYSSEY-HCM (CV027031) (Nonobstructive hypertrophic cardiomyopathy [nHCM])

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the applications, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the products is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of these products in the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK (Great Britain) versions of the SmPCs and PIL for these products are available on the MHRA website.

IX. TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N