SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR MAVACAMTEN (CAMZYOS®)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of CAMZYOS® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, eg, by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of CAMZYOS® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bristol-Myers Squibb SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of CAMZYOS®.

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1 SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the risk management plan (RMP) for CAMZYOS.The RMP details important risks of CAMZYOS, how these risks can be minimised, and how more information will be obtained about CAMZYOS's risks and uncertainties (missing information).

CAMZYOS's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how CAMZYOS should be used.

This summary of the RMP for CAMZYOS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of CAMZYOS's RMP.

1.1 The Medicine and What It Is Used For

CAMZYOS is authorised for the treatment of symptomatic (New York Heart Association, NYHA, Class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see SmPC for the full indication). It contains mavacamten as the active substance and it is given by oral administration.

Further information about the evaluation of CAMZYOS's benefits can be found in CAMZYOS's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/what-we-publishwhen/european-public-assessment-reports-background-context.

1.2 Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of CAMZYOS, together with measures to minimise such risks and the proposed studies for learning more about CAMZYOS's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size − the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status − the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of CAMZYOS, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PBRER assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of CAMZYOS is not yet available, it is listed under 'missing information' below.

1.2.1 List of Important Risks and Missing Information

Important risks of CAMZYOS are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CAMZYOS. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 1.2.1-1: List of Important Risks and Missing Information

Important identified risks	None
Important potential risks	• Heart failure due to systolic dysfunction defined as symptomatic LVEF <50% • Heart failure due to overexposure to mavacamten resulting from interaction with CYP 2C19 and strong 3A4 inhibitors • Embryofoetal 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

1.2.2 Summary of Important Risks

Table 1.2.2-1: Important Potential Risks

Heart failure due to systolic dysfunction defined as symptomatic LVEF <50%	
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.

Table 1.2.2-1: Important Potential Risks

Heart failure due to systolic dysfunction defined as symptomatic LVEF <50%	
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. 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 CYP2 C19 inhibitors or strong 3A4 inhibitors.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 Additional risk minimization measures: • HCP Guide • 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) • VALOR-HCM (MYK-461-017) • DISCOVER-HCM (CV027012)
Heart failure due to overexposure to mavacamten resulting from interaction with CYP 2C19 and strong 3A4 inhibitors	
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 CYP 2C19 and 3A4 and increased mavacamten concentrations in the presence of CYP 2C19 and strong 3A4 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 LVEF to <50% (median 48%: range 35 to 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 strong CYP 3A4 inhibitors (prescription drugs, over the counter [OTC] medications, herbal products).
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.5 Additional risk minimization measures: • HCP Guide • HCP Checklist

Table 1.2.2-1: Important Potential Risks

Heart failure due to systolic dysfunction defined as symptomatic LVEF <50%	
	• 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) • VALOR-HCM (MYK-461-017) • DISCOVER-HCM (CV027012) See Section 1.3 of this summary for an overview of the post-authorisation development plan.
Embryofoetal 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 minimization measures	Routine risk minimization measures: SmPC Section 4.4, 4.6, and 5.3 Additional risk minimisation measures: • HCP Guide • HCP Checklist • Patient Card and Patient Guide

Table 1.2.2-2: Missing Information

Patients with Class IV NYHA	
Risk minimization measures	Routine risk minimization 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) • VALOR-HCM (MYK-461-017) See Section 1.3 of this summary for an overview of the post-authorisation development plan.
Patients being treated with disopyramide	
Risk minimization measures	Routine risk minimization 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) • DISCOVER-HCM (CV027012)

Table 1.2.2-2: Missing Information

	• VALOR-HCM (MYK-461-017) See Section 1.3 of this summary for an overview of the post-authorisation development plan.
Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)	
Risk minimization measures	Routine risk minimization 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) • DISCOVER-HCM (CV027012) • VALOR-HCM (MYK-461-017) See Section 1.3 of this summary for an overview of the post-authorisation development plan.
Long-term safety, including detrimental CV effects	
Risk minimization measures	Routine risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (PASS; CV027013) • DISCOVER-HCM (CV027012) • MAVA-LTE (MYK-461-007) • VALOR-HCM (MYK-461-017) • Planned meta-analysis to assess CV outcome safety See Section 1.3 of this summary for an overview of the post-authorisation development plan.
Use during lactation	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.6 Additional risk minimization measures: • HCP Guide • Patient Guide

1.3 Post-authorisation Development Plan

1.3.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of CAMZYOS.

1.3.2 Other Studies in Post-authorisation Development Plan

Table 1.3.2-1: Category 3 Ongoing and Planned Additional Pharmacovigilance Activities

Study Short Name and Title	Rationale and Study Objectives
CV027013: Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe	The primary objectives of this study are to: • Estimate the incidence rate of heart failure with systolic dysfunction (defined as worsening symptomatic status with LVEF <50%) among adult patients with oHCM who received mavacamten or non-mavacamten treatment during the study period. • Estimate the incidence rate of heart failure with systolic dysfunction among adult patients with oHCM who received mavacamten or non-mavacamten treatment during the study period - AND - who received a concomitant CYP 2C19 inhibitor and/or strong CYP 3A4 inhibitor. • Estimate the incidence rate of MACE; a composite endpoint consisting of acute myocardial infarction, stroke, hospitalization due to heart failure, and cardiovascular mortality, of the individual components of MACE and of all-cause mortality among adult patients with oHCM who received mavacamten or non-mavacamten treatment during the study period. • Estimate the incidence rate of arrhythmia (defined as atrial fibrillation, atrial flutter, sustained ventricular tachycardia, and/or ventricular arrhythmia) among adult patients with oHCM who received mavacamten or non-mavacamten treatment during the study period. • Compare the risk of heart failure with systolic dysfunction, of MACE (as composite endpoint and individual component endpoints), of all-cause mortality, and of arrhythmia among adult patients with oHCM who received mavacamten to those patients who received non-mavacamten treatment. The secondary objectives of this study are to: • Estimate the incidence rate of heart failure with systolic dysfunction, of MACE (as composite endpoint and individual endpoints), of all-cause mortality, and of arrhythmia among adult patients with oHCM who received mavacamten during the study period - AND - who had concomitant use of single or combination use of the following medications: - disopyramide and/or - β-blockers and/or non-dihydropyridine calcium-channel blockers (verapamil/diltiazem) • Assess changes in clinical responses from baseline (as measured by changes in NYHA class, LVOT gradient, LVEF, and N-terminal-pro B-type natriuretic peptide (BNP) at select time points for adult patients with oHCM who received mavacamten or non-mavacamten treatment duringthe study period.

Table 1.3.2-1: Category 3 Ongoing and Planned Additional Pharmacovigilance Activities

Study Short Name and Title	Rationale and Study Objectives
	The exploratory objective of this study is to: • Assess the primary and secondary objectives in a subset of adult patients with oHCM - AND - NYHA Class IV functional classification and preserved LVEF (>55%) at baseline who received mavacamten or non-mavacamten treatment during the study period.
MYK-461-007 - A Long-term Safety Extension Study of Mavacamten in Adults with Hypertrophic Cardiomyopathy Who Have Completed the MAVERICK-HCM or EXPLORER-HCM Trials	The primary objective of this study is as follows: • To assess the long-term safety and tolerability of mavacamten in participants with HCM previously enrolled in 1 of 2 placebo-controlled trials: MAVERICK-HCM for non-obstructive HCM (nHCM) and EXPLORER-HCM for obstructive HCM (oHCM) The secondary objectives of this study are as follows: • To assess the long-term effects of mavacamten on symptoms and echocardiographic measures of cardiac function • To assess left ventricular outflow tract (LVOT) obstruction as determined by Doppler echocardiography in the EXPLORER-LTE Cohort The exploratory objective of this study was as follows: • To assess the long-term effects of mavacamten on disease biomarker
MYK-461-017 - A Randomized, Double-blind, Placebo-controlled Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Who Are Eligible for Septal Reduction Therapy	This is a randomized, double-blind, placebo-controlled, multi-center study in the United States (U.S.) that will evaluate the effect of mavacamten treatment on reducing the number of septal reduction therapy (SRT) procedures performed in subjects with symptomatic obstructive hypertrophic cardiomyopathy (oHCM [also known as HOCM]) who are eligible for SRT based on ACCF/AHA 2011 and/or ESC 2014 guidelines.
CV027012 (DISCOVER-HCM) - Deliver Insights in Hypertrophic Cardiomyopathy and Observational Outcomes in Real-world: United States Prospective Registry Study	This is an observational, multicenter registry of prospectively enrolled adult patients with symptomatic (NYHA functional class II-IV) oHCM in the US and Puerto Rico and LVEF ≥ 55% at enrollment. The registry aims to recruit an estimated 50 sites in the US and Puerto Rico to enroll approximately 1,500 patients with oHCM including at least 700 patients initiating treatment with mavacamten at enrollment, once it is available. Enrollment is estimated to require two years.
Planned Meta-analysis to assess CV outcome safety	A meta-analysis of all existing and upcoming placebo-controlled mavacamten studies to quantify detriment in CV risk compared to placebo on top of standard of care.