CAMZYOS® (mavacamten)

Healthcare Professional Guide

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Bristol Myers Squibb™

INTRODUCTION

This guide contains specific information on the safe prescribing and use of CAMZYOS (mavacamten). This guide contains the following information:

- Details on the mechanism of action of CAMZYOS and dosing information
- Details on the risks of
  - Heart failure due to systolic dysfunction
  - Heart failure due to drug interactions with cytochrome P450 (CYP) 2C19 inhibitors and moderate or strong CYP3A4 inhibitors
  - Embryo-fetal toxicity
- Information about educational materials that healthcare professionals (HCPs) should distribute to patients and/or their caregiver(s)
- Contact details for reporting adverse events and pregnancies in patients receiving CAMZYOS and where to find additional information
- A **Treating and Counseling Checklist** to ensure that HCPs, patients and/or their caregiver(s) are aware of the steps they need to take for safe use of CAMZYOS
- Further details are available in the Full Prescribing Information

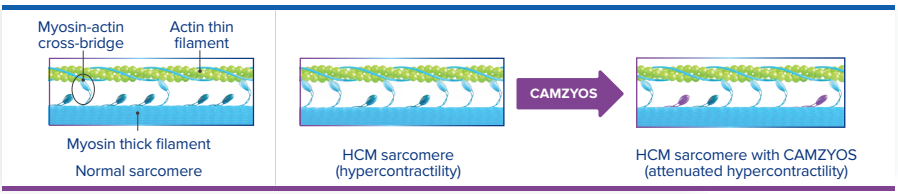
THERAPEUTIC INDICATION

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

MECHANISM OF ACTION OF CAMZYOS

CAMZYOS is a selective, allosteric and reversible cardiac myosin inhibitor. It modulates the number of myosin heads that can enter power-generating states, thus reducing the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation. CAMZYOS also shifts the overall myosin population towards an energy-sparing, but recruitable, super-relaxed state (see Figure 1). Excess myosin actin cross-bridge formation and dysregulation of the super-relaxed state of myosin are mechanistic hallmarks of HCM, which can result in hypercontractility, impaired relaxation, excess energy consumption and myocardial wall stress.

Figure 1: Mechanism of Action



In patients with HCM, there is excessive availability of myosin heads ready to form cross-bridges with actin, with a reduced proportion remaining in the energy-sparing super-relaxed state not available for engagement. This results in myocardial hyper-contractility and consequent pathophysiological abnormalities such as hypertrophy, diastolic impairment, left ventricular outflow tract (LVOT) obstruction, arrhythmias, and fibrosis.

Myosin inhibition with CAMZYOS counters this state of things by reducing the number of myosin heads available for engagement with actin thus returning to a normal contractile state. This reduces dynamic LVOT obstruction, improves cardiac filling pressures and biomarkers of cardiac stress, and improves symptoms and exercise capacity.

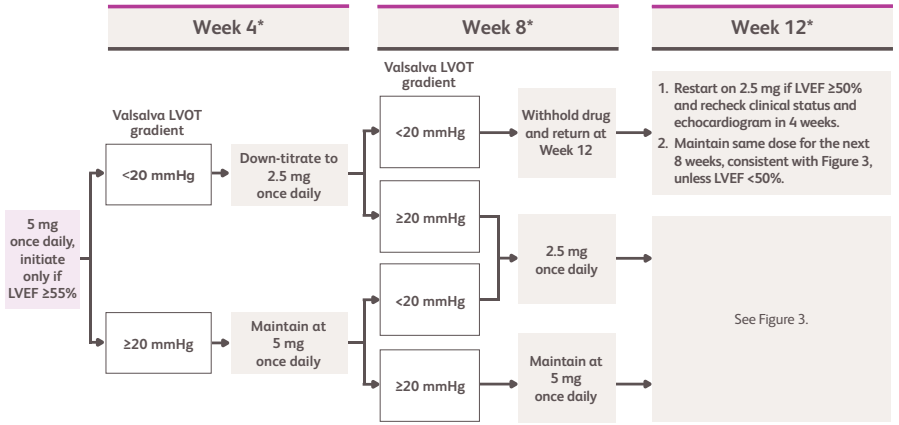
TREATMENT AND DOSING

Initiation, Maintenance, and Interruption of Treatment

- Confirm absence of pregnancy and usage of effective contraception in females of reproductive potential.
- Initiation or up-titration of CAMZYOS in patients with LVEF <55% is not recommended
- The recommended starting dose is 5 mg once daily without regard to food; allowable subsequent doses with titration are 2.5, 5, 10, or 15 mg once daily.
- Patients may develop heart failure while taking CAMZYOS. Regular LVEF and Valsalva left ventricular outflow tract (LVOT) gradient assessment is required for careful titration to achieve an appropriate target Valsalva LVOT gradient, while maintaining LVEF ≥50% and avoiding heart failure symptoms (see Figure 2 and Figure 3).
- Additional assessment of LVEF is recommended if clinical status changes or in patients with a serious intercurrent illness such as infection or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia).
- Daily dosing takes weeks to reach steady-state drug levels and therapeutic effects, and genetic variation in metabolism and drug interactions can cause large differences in exposure.
- When initiating or titrating CAMZYOS, first consider LVEF then consider the Valsalva LVOT gradient and patient clinical status to guide appropriate CAMZYOS dosing. Follow the algorithms for Initiation (Figure 2) and Maintenance (Figure 3) for appropriate CAMZYOS dosing and monitoring schedules.
- If LVEF <50% while taking CAMZYOS, interrupt treatment. Follow the algorithm for Interruption (Figure 4) for guidance on interrupting, restarting, or discontinuing CAMZYOS. If interrupted at 2.5 mg, either restart at 2.5 mg or discontinue permanently.

TREATMENT AND DOSING (continued)

Figure 2: Treatment Initiation



*Interrupt treatment if LVEF <50% at any clinic visit; restart treatment after 4 weeks if LVEF ≥50%. See Figure 4.

Figure 3: Treatment Maintenance

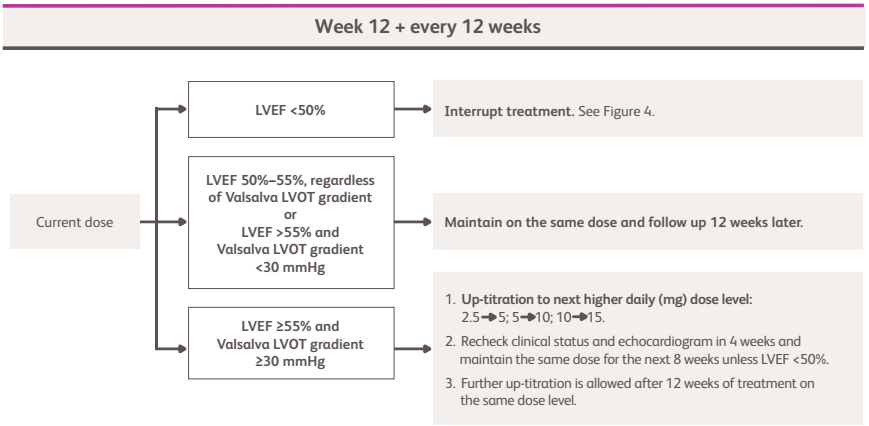
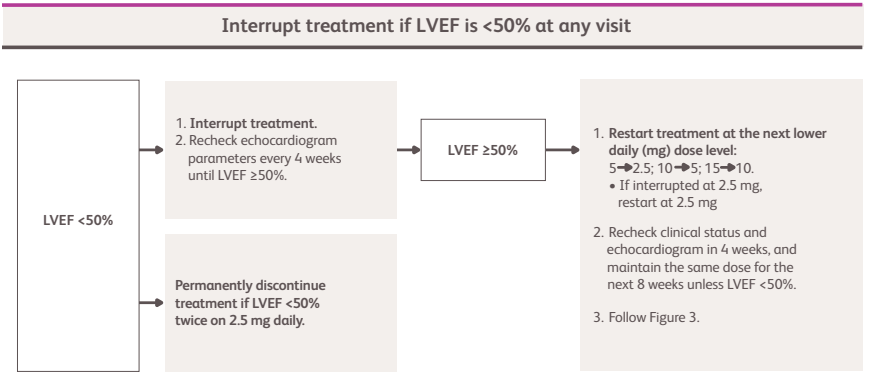


Figure 4: Treatment Interruption



TREATMENT AND DOSING (continued)

Concomitant therapy with CYP2C19 or CYP3A4 inducers or inhibitors
It is recommended that patients who are initiated or have their treatment modified with medicines and products that are inhibitors or inducers of CYP450 follow the guidance below.

CAMZYOS is contraindicated with concomitant use of:

- Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors
- Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers

Initiate CAMZYOS at the recommended starting dosage of 5 mg orally once daily in patients who are on stable therapy with a weak CYP2C19 or a moderate CYP3A4 inhibitor.

Reduce dosage of CAMZYOS by one level (i.e., 15 →10 mg; 10 →5 mg; or 5 →2.5 mg) in patients who initiate a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor. Schedule clinical and echocardiographic assessment 4 weeks after inhibitor initiation, and do not up-titrate CAMZYOS until 12 weeks after inhibitor initiation. Avoid initiation of concomitant weak CYP2C19 and moderate CYP3A4 inhibitors in patients who are on stable treatment with 2.5 mg of CAMZYOS because a lower CAMZYOS once-daily dose is not available.

RISKS ASSOCIATED WITH CAMZYOS

Risk of heart failure due to systolic dysfunction

A reduction in LVEF is an expected on-target effect of CAMZYOS. This LVEF effect is generally small (mean reduction of 4% in the pivotal Phase 3 trial of CAMZYOS [N=251]) and contributes to the efficacy of treatment with CAMZYOS. Some patients may see a decrease in their LVEF to <50% due to an excess medicinal effect of CAMZYOS, which may lead to heart failure.

Risk factors and groups

Patients with a serious intercurrent illness such as serious infection or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia) may be at greater risk of developing systolic dysfunction and heart failure.

Risk mitigation

Assess the patient's clinical status and LVEF prior to and regularly during treatment and adjust the dose of CAMZYOS accordingly. New or worsening arrhythmia, dyspnea, chest pain, fatigue, palpitations, leg edema or elevations in N-terminal pro hormone b-type natriuretic peptide (NT-proBNP) may be signs and symptoms of heart failure and should also prompt an evaluation of cardiac function.

Advise patients to report any signs or symptoms of heart failure (described above) **immediately** to their HCP or seek medical attention. Regular echocardiograms must be performed, as described in the **Treatment and Dosing** section of this guide, in order to mitigate the risk of heart failure. Please see CAMZYOS local Prescribing Information for additional information.

In the presence of intercurrent illnesses, such as infections or arrhythmias that may impair systolic function, dose increases are not recommended.

RISKS ASSOCIATED WITH CAMZYOS (continued)

Risk of heart failure due to drug interactions with CYP2C19 inhibitors and moderate or strong CYP3A4 inhibitors

CAMZYOS is primarily metabolized by CYP2C19 and (to a lesser extent) CYP3A4 enzymes. Co-administration or discontinuation of CYP2C19 inhibitors or moderate to strong CYP3A4 inhibitors may alter the plasma concentration of CAMZYOS. Starting or increasing the dose of any CYP2C19 inhibitor or a moderate to strong CYP3A4 inhibitor may increase the risk of heart failure due to systolic dysfunction; conversely, discontinuation or decreasing the dose of these inhibitor types may lead to loss of response to CAMZYOS.

Risk factors and groups

Patients treated with CYP2C19 inhibitors or moderate or strong CYP3A4 inhibitors.

Risk mitigation

HCPs should consider, **prior to and throughout treatment**, the potential for drug interactions involving CAMZYOS, including those arising from coadministration with over-the-counter medications (such as omeprazole or esomeprazole) and herbal supplements. CAMZYOS is contraindicated with concomitant use of moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors. Refer to section Concomitant therapy with CYP2C19 or CYP3A4 inducers or inhibitors for guidance on CAMZYOS dose adjustment and LVEF monitoring recommendations when initiating or changing the dose of a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor.

Examples of CYP2C19 inhibitors and moderate/strong CYP3A4 inhibitors are shown in Table 2. Please be aware that **this is not an exhaustive list** of CYP2C19 inhibitors or moderate/strong CYP3A4 inhibitors nor their indications. Intermittent use of products that might interact with CAMZYOS, including prescription and over-the-counter medications, herbal supplements and grapefruit juice, is not recommended.

Table 2: Examples of CYP2C19 inhibitors and moderate/strong CYP3A4 inhibitors

Inhibitor	Medicines/products	Condition treated
CYP2C19 inhibitors	Felbamate, carbamazepine	Epilepsy
	Chloramphenicol	Bacterial infections
	Fluoxetine, fluvoxamine	Depression and OCD
	Fluconazole, voriconazole	Fungal infections
	Omeprazole, esomeprazole, cimetidine	Gastric ulcers and acid reflux
Moderate CYP3A4 inhibitors	Verapamil, diltiazem	Heart conditions
	Erythromycin	Bacterial infections
Strong CYP3A4 inhibitors	Clarithromycin	Bacterial infections
	Itraconazole, ketoconazole, posaconazole, voriconazole	Fungal infection
	Paritaprevir	Hepatitis C
	Ritonavir (usually given in combination with other anti-HIV or anti-hepatitis C drugs)	Hepatitis C and HIV
	Cobicistat, elvitegravir, lopinavir, saquinavir, tipranavir	HIV
	Grapefruit juice	

CYP=cytochrome P450; HIV=human immunodeficiency virus; OCD=obsessive compulsive disorder.
Information adapted from the Food and Drug Administration, 2020; Park, 2003; and Orlando, 2003.

Inform the patient that they **must** consult their prescribing HCP and pharmacist prior to taking any new medications or herbal supplements, changing the dose or stopping any medications or herbal supplements they may currently be taking.

RISKS ASSOCIATED WITH CAMZYOS (continued)

Embryo-fetal toxicity

CAMZYOS may cause embryo-fetal harm when administered to a pregnant patient based on pregnancy data from animal studies. There are no data on the use of CAMZYOS in pregnant patients. CAMZYOS should **not** be used during pregnancy.

Risk factors and groups

Pregnant patients and patients of childbearing potential without using highly effective contraception.

Risk mitigation

Prior to treatment initiation, confirm a negative pregnancy test in patients of childbearing potential. Inform the patient about the risk of embryo-fetal toxicity associated with CAMZYOS and counsel the patient on the need to avoid pregnancy. Recommend use of a highly effective form of contraception during treatment and for 4 months after the last dose is administered.

Please instruct the patient to inform you if they are pregnant or suspect they are pregnant **immediately**. If, at any point, a patient becomes pregnant while receiving CAMZYOS, inform the patient of the potential risk to the fetus.

ADDITIONAL INFORMATION

A **Patient Guide** and **Patient Card** are available for you to aid in counseling of, and to provide to patients and/or their caregiver(s).

Please ensure patients and/or their caregiver(s) are counseled appropriately, including on the following key safety messages:

- The risks associated with CAMZYOS and when to seek medical attention
- The importance of and requirements for echocardiogram assessment prior to and during treatment
- The importance of informing their HCPs of all medications and herbal and supplements the patient is taking

Please inform patients to carry the **Patient Card** with them at all times. A copy of this card is embedded in the **Patient Guide**. Advise patients to tell any HCP that sees them that they are taking CAMZYOS.

A checklist is provided at the end of this guide to support HCPs when treating patients receiving CAMZYOS and counseling patients and/or their caregiver(s).

REPORTING ADVERSE EVENTS

The safe use of CAMZYOS is of paramount importance. As part of our ongoing safety monitoring, Bristol Myers Squibb (BMS) wishes to be informed of adverse events that have occurred during use of CAMZYOS. Please report any adverse events and pregnancies to BMS at: < MedInfo.Singapore@bms.com> or 1800 415 5182, or to Vigilance and Compliance Branch, Health Products Regulation Group, Health Sciences Authority at Tel: 6866 1111, or report online at https://www.hsa.gov.sg/adverse-events.

REFERENCE LIST

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HEALTHCARE PROFESSIONAL CHECKLIST

The checklist below includes information to consider when treating patients receiving CAMZYOS and counseling patients and/or their caregiver(s). **Please note that this checklist is not meant to be all-inclusive.**

Prior to starting treatment

- ☐ Obtain a medical history from the patient to determine risk factors for heart failure.
- ☐ Complete an echocardiogram to confirm that the patient's LVEF is ≥55% prior to initiating CAMZYOS.
- ☐ Assess for potential drug interactions involving CAMZYOS and any drug (including prescription and over-the-counter medications, herbal supplements and grapefruit juice).
- ☐ Inform the patient of the risk of heart failure associated with CAMZYOS and that they must consult their HCP or seek medical attention immediately if they experience worsening, persistent or new shortness of breath, chest pain, fatigue, palpitations or leg swelling.
- ☐ Counsel the patient on the risks of potential drug interactions involving CAMZYOS and not to start or stop taking any medications or change the dose of any medication they are taking without talking to you first.
- ☐ Confirm a negative pregnancy test in patients of childbearing potential.
- ☐ Educate patients of childbearing potential on the risk of embryo-fetal toxicity associated with CAMZYOS. Counsel on the need to avoid pregnancy and the need for an effective form of contraception during treatment with CAMZYOS and for 4 months following discontinuation.
- ☐ Instruct patients of childbearing potential to contact you or another member of your healthcare team **immediately** if they become pregnant or suspect they may be pregnant.
- ☐ Provide the patient with the **Patient Guide** and highlight the **Patient Card** within the guide.
- ☐ Schedule the next echocardiogram 4 weeks after initiation of treatment.

During treatment at each clinical visit (as described in the Prescribing Information).

- ☐ Confirm LVEF is ≥50% by echocardiogram assessment. If at any visit LVEF is <50%, interrupt treatment for 4 weeks and until LVEF is ≥50%.
- ☐ Assess the LVOT gradient with the Valsalva maneuver and adjust the dose per the guidance provided in the Prescribing Information.
- ☐ Assess the patient for signs and symptoms of heart failure.
- ☐ Assess for intercurrent illnesses such as infections or arrhythmia (e.g., atrial fibrillation or other uncontrolled tachyarrhythmia).
- ☐ Assess for drug interactions involving CAMZYOS and any drug (including prescription and over-the-counter medications, herbal supplements and grapefruit juice) that the patient has newly started, has changed the dose of or plans on taking in the future.
- ☐ Counsel the patient on the risks of potential drug interactions involving CAMZYOS.
- ☐ Remind the patient of the risks associated with CAMZYOS and that they must consult their HCP or seek medical attention immediately if they experience worsening, persistent or new shortness of breath, chest pain, fatigue, palpitations or leg swelling.
- ☐ Counsel the patient on actions to take in case of an overdose and missed or delayed doses.
- ☐ Remind patients of childbearing potential of the risk of embryo-fetal toxicity associated with CAMZYOS. Counsel on the need to avoid pregnancy and the need for an effective form of contraception during treatment and for 4 months following discontinuation.
- ☐ Periodically check pregnancy status throughout treatment in patients of childbearing potential.
- ☐ Instruct patients of childbearing potential to contact you or another member of your healthcare team **immediately** if they become pregnant or suspect they may be pregnant.
- ☐ Provide the patient with the **Patient Guide** and **Patient Card** if needed.
- ☐ Schedule the next echocardiogram per the instructions provided in the Prescribing Information.

After treatment

- ☐ Counsel patients of childbearing potential on the need to avoid pregnancy and the need for a highly effective form of contraception for 4 months following discontinuation of CAMZYOS.

NOTES

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