CAMZYOS® (mavacamten)

Healthcare Professional Guide

Bristol Myers Squibb®

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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.
  - For the full prescribing information please refer to the Israeli Prescribing Information.

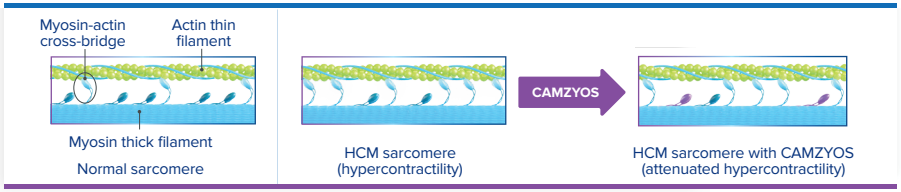
THERAPEUTIC INDICATION

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. CAMZYOS 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. CAMZYOS also shifts the overall myosin population towards an energy-sparing, but recruitable, super-relaxed state (see Figure 1).
Excess 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, myosin inhibition with CAMZYOS normalizes contractility, reduces dynamic left ventricular outflow tract (LVOT) obstruction and improves cardiac filling pressures and biomarkers of cardiac stress, improving symptoms and exercise capacity.

TREATMENT AND DOSING

Before starting treatment

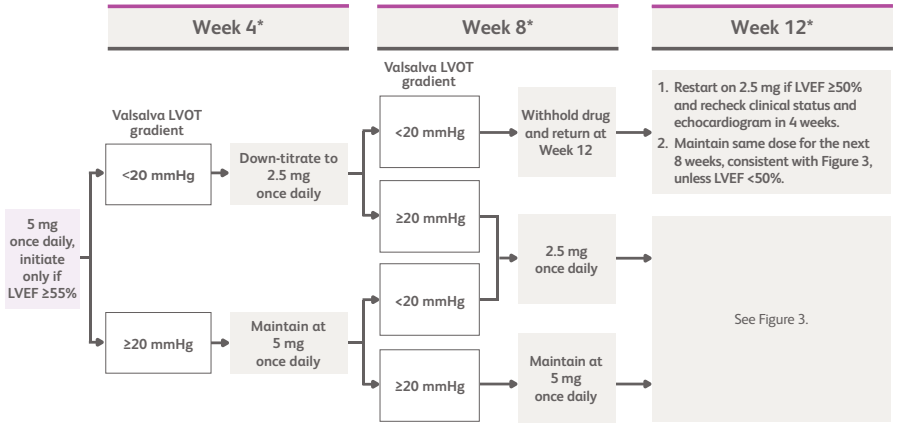
- Confirm a negative pregnancy test and advise patients of reproductive potential to use an effective contraception during treatment with CAMZYOS and for 4 months following discontinuation
- Assess left ventricular ejection fraction (LVEF) by echocardiogram. Do not initiate CAMZYOS in patients with LVEF <55%
- Consider contraindications and drug interactions prior to and throughout treatment

During treatment

- The recommended starting dose of CAMZYOS is 5 mg orally once daily. CAMZYOS may be taken without regard to food. If a dose is missed, it should be taken as soon as possible, and the next scheduled dose should be taken at the usual time the following day. Exact timing of dosing during the day is not essential, but two doses should not be taken on the same day. Swallow capsules whole. Do not break, open or chew the capsule
- Assess patient response to treatment, including LVOT gradient with Valsalva maneuver and LVEF, at Weeks 4, 8 and 12 and every 12 weeks thereafter. Additional echocardiograms may be required if there is a dose change or treatment interruption, as described in Figures 3 and 4. Adjust the dose based on Figures 2–4
- Patients may develop heart failure while taking CAMZYOS. Regular LVEF and LVOT gradient with Valsalva maneuver assessments are required for careful dose titration to achieve an appropriate target LVOT gradient with Valsalva maneuver while maintaining LVEF ≥50% and avoiding heart failure symptoms (see Figure 2 and Figure 3)
- Dose increases should not occur more frequently than every 12 weeks. Do not up-titrate CAMZYOS in patients with LVEF <55% or those experiencing an intercurrent illness such as infections or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmias) that may impair systolic function. Interrupt treatment if LVEF is <50% at any visit; restart treatment after 4 weeks if LVEF is ≥50% (see Figure 4)

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

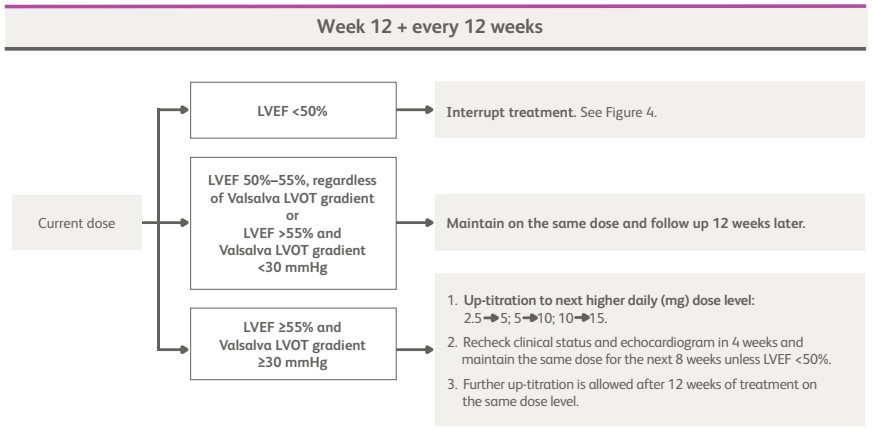
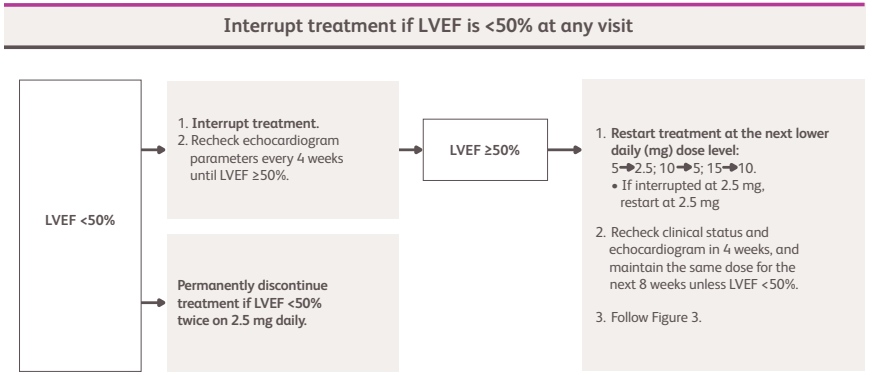


Figure 4: Treatment Interruption



TREATMENT AND DOSING (continued)

Concomitant therapy

It is recommended that patients who initiate or modify treatment with medicines and products that are inhibitors or inducers of CYP450 follow the guidance in Table 1.

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

Table 1: CAMZYOS dose modification and monitoring with concomitant medicinal products

Effect on CYP activity	Concomitant medicine/product	Dosage modification and monitoring
Inhibitors	**Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors**	• Concomitant use with CAMZYOS is contraindicated
	Weak CYP2C19 or moderate CYP3A4 inhibitors	• Reduce dosage of CAMZYOS by one level 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 2.5mg of CAMZYOS because a lower CAMZYOS once-daily dose is not available.
Inducers	**Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers**	• Concomitant use with CAMZYOS is contraindicated.

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) are at greater risk of developing systolic dysfunction and heart failure.

Risk mitigation

Assess patients presenting with signs and symptoms of systolic dysfunction, including new or worsening arrhythmia, dyspnea, chest pain, fatigue, palpitations, leg edema or elevations in N-terminal pro B-type natriuretic peptide (NT-proBNP), and promptly evaluate 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 Israeli Prescribing Information for additional information.

In the presence of intercurrent illnesses, such as infections or arrhythmias that may impair systolic function, delay dose increases.

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.

Concomitant use with a moderate to strong CYP2C19 or a strong CYP3A4 inhibitor increases CAMZYOS exposure, which may increase the risk of heart failure due to systolic dysfunction.

Concomitant use with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor increases CAMZYOS exposure, which may increase the risk of adverse drug reactions.

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 and esomeprazole) and herbal supplements. CAMZYOS is contraindicated in patients using moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors. Refer to Table 1 for guidance on CAMZYOS dose adjustment and clinical/echocardiographic assessment recommendations when initiating a weak CYP2C19 or moderate CYP3A4 inhibitor.

Examples of drugs that are contraindicated or that require dose adjustment of CAMZYOS upon initiation 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.

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

Inhibitor	Medicines/products	Condition treated
CYP2C19 inhibitors	Carbamazepine	Epilepsy
	Chloramphenicol	Bacterial infections
	Fluoxetine, fluvoxamine	Depression and OCD
	Fluconazole, voriconazole	Fungal infections
	Omeprazole, esomeprazole	Gastric ulcers and acid reflux
Moderate CYP3A4 inhibitors	Verapamil, diltiazem	Heart conditions
Strong CYP3A4 inhibitors	Clarithromycin, erythromycin	Bacterial infections
	Itraconazole, ketoconazole, posaconazole, voriconazole	Fungal infection
	Ritonavir (usually given in combination with other anti-HIV or anti-hepatitis C drugs)	Hepatitis C and HIV
	Cobicistat, elvitegravir, lopinavir	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. Advise females of reproductive potential and pregnant females about the potential risk to the fetus with maternal exposure to CAMZYOS during pregnancy.

Risk factors and groups
Pregnant patients and patients of childbearing potential not using 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 advise patients to use an effective form of contraception during treatment with CAMZYOS and for 4 months after the last dose is administered. Combined hormonal contraceptives (CHCs) containing a combination of ethinyl estradiol and norethindrone may be used with mavacamten. However, CAMZYOS may reduce the effectiveness of certain other CHCs. If these CHCs are used, advise patients to add nonhormonal contraception (such as condoms) during concomitant use and for 4 months after the last dose of CAMZYOS.

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.

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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 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 in treating patients receiving CAMZYOS and counseling patients and/or their caregiver(s).

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REPORTING ADVERSE EVENTS

The safe use of CAMZYOS is of paramount importance. As part of our ongoing safety monitoring, Bristol Myers Squibb wishes to be informed of adverse events that have occurred during use of CAMZYOS. Please report any adverse events and pregnancies to:

- **BMS Israel** via email: medinfo.Israel@bms.com
  or phone: 1809-388054 (A toll-free number).
- **The Israeli Ministry of Health** by using the online form for reporting adverse events on the Home page of the Ministry of health website: www.health.gov.il
  or by entering the following link: https://sideeffects.health.gov.il

CONTACT DETAILS

If you have any questions regarding CAMZYOS or require more information, please contact Bristol Myers Squibb.

Telephone: 1809-388054 (a toll-free number)

Email: medinfo.Israel@bms.com

To obtain a copy of this HCP Guide / Patient Guide and Card, please contact BMS by phone 03-5231021 or fax 03-9226896

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References:

1. Drug development and drug interactions: table of substrates, inhibitors and inducers. U.S. Food and Drug Administration. Updated March 10, 2020. Accessed July 7, 2022. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
2. Park JY, Kim KA, Kim SL. Chloramphenicol is a potent inhibitor of cytochrome P450 isoforms CYP2C19 and CYP3A4 in human liver microsomes. *Antimicrob Agents Chemother*. 2003;47(11):3463-3469.
3. Orlando R, Piccoli P, De Martin S, Padrini R, Palatini P. Effect of the CYP3A4 inhibitor erythromycin on the pharmacokinetics of lignocaine and its pharmacologically active metabolites in subjects with normal and impaired liver function. *Br J Clin Pharmacol*. 2003;55(1):86-93.

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HEALTHCARE PROFESSIONAL CHECKLIST

The checklist below includes information to consider when treating patients receiving CAMZYOS and counselling 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 arrythmia, shortness of breath, chest pain, fatigue, palpitations, leg swelling or rapid weight gain.
- ☐ Counsel the patient on the risks of potential drug interactions involving CAMZYOS and to not 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 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 Israeli 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 Israeli 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 arrythmia, shortness of breath, chest pain, fatigue, palpitations, leg swelling, or rapid weight gain.
- ☐ 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 for an effective form of contraception during treatment with CAMZYOS 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 Israeli Prescribing Information.

After treatment

- ☐ Counsel patients of childbearing potential on the need for an effective form of contraception for 4 months following discontinuation of CAMZYOS.

NOTES

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