ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CAMZYOS 2.5 mg hard capsules

Each hard capsule contains 2.5 mg of mavacamten.

CAMZYOS 5 mg hard capsules

Each hard capsule contains 5 mg of mavacamten.

CAMZYOS 10 mg hard capsules

Each hard capsule contains 10 mg of mavacamten.

CAMZYOS 15 mg hard capsules

Each hard capsule contains 15 mg of mavacamten.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule)

CAMZYOS 2.5 mg hard capsules

Light purple opaque cap imprinted with “2.5 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction. Capsule size of approximately 18.0 mm in length.

CAMZYOS 5 mg hard capsules

Yellow opaque cap imprinted with “5 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction. Capsule size of approximately 18.0 mm in length.

CAMZYOS 10 mg hard capsules

Pink opaque cap imprinted with “10 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction. Capsule size of approximately 18.0 mm in length.

CAMZYOS 15 mg hard capsules

Grey opaque cap imprinted with “15 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction. Capsule size of approximately 18.0 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CAMZYOS is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the management of patients with cardiomyopathy.

Before treatment initiation, patients' left ventricular ejection fraction (LVEF) should be assessed by echocardiography (see section 4.4). If LVEF is < 55%, treatment should not be initiated.

Before initiation of treatment, women of childbearing potential must have a negative pregnancy test (see sections 4.4 and 4.6).

Patients should be genotyped for Cytochrome P450 (CYP) 2C19 (CYP2C19) in order to determine appropriate mavacamten dose. Patients with CYP2C19 poor metaboliser phenotype may have increased mavacamten exposures (up to 3 times) that can lead to increased risk of systolic dysfunction compared to normal metabolisers (see sections 4.4 and 5.2). If treatment initiation occurs prior to determination of CYP2C19 phenotype, patients should follow dosing instructions for poor metabolisers (see figure 1 and 3 and table 1) until CYP2C19 phenotype is determined.

Posology

The dose range is 2.5 mg to 15 mg (either 2.5 mg, 5 mg, 10 mg or 15 mg).

CYP2C19 poor metaboliser phenotype
The recommended starting dose is 2.5 mg orally once daily. The maximum dose is 5 mg once daily. The patient should be assessed for early clinical response by left ventricular outflow tract (LVOT) gradient with Valsalva manoeuvre 4 and 8 weeks after treatment initiation (see figure 1).

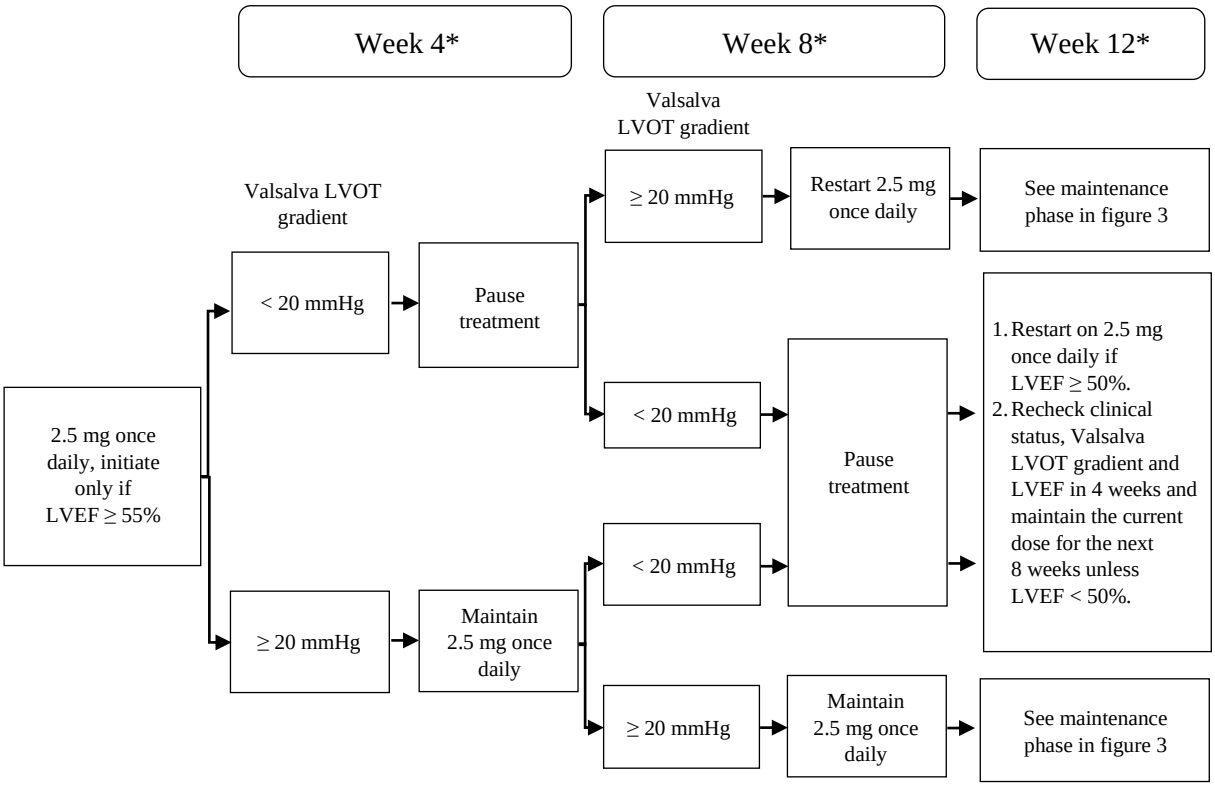
CYP2C19 intermediate, normal, rapid and ultra-rapid metaboliser phenotype
The recommended starting dose is 5 mg orally once daily. The maximum dose is 15 mg once daily. The patient should be assessed for early clinical response by LVOT gradient with Valsalva manoeuvre 4 and 8 weeks after treatment initiation (see figure 2).

Once an individualised maintenance dose is achieved with LVEF ≥ 55%, patients should be assessed every 6 months. For patients with LVEF 50 - < 55% regardless of Valsalva LVOT gradient, patients should be assessed every 3 months (see figure 3). If at any visit the patient's LVEF is < 50%, the treatment should be interrupted for 4 weeks and until LVEF returns to ≥ 50% (see figure 4).

In patients experiencing an intercurrent illness such as serious infection or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia) which may impair systolic function, LVEF assessment is recommended, and dose increases are not recommended until intercurrent illness is resolved (see section 4.4).

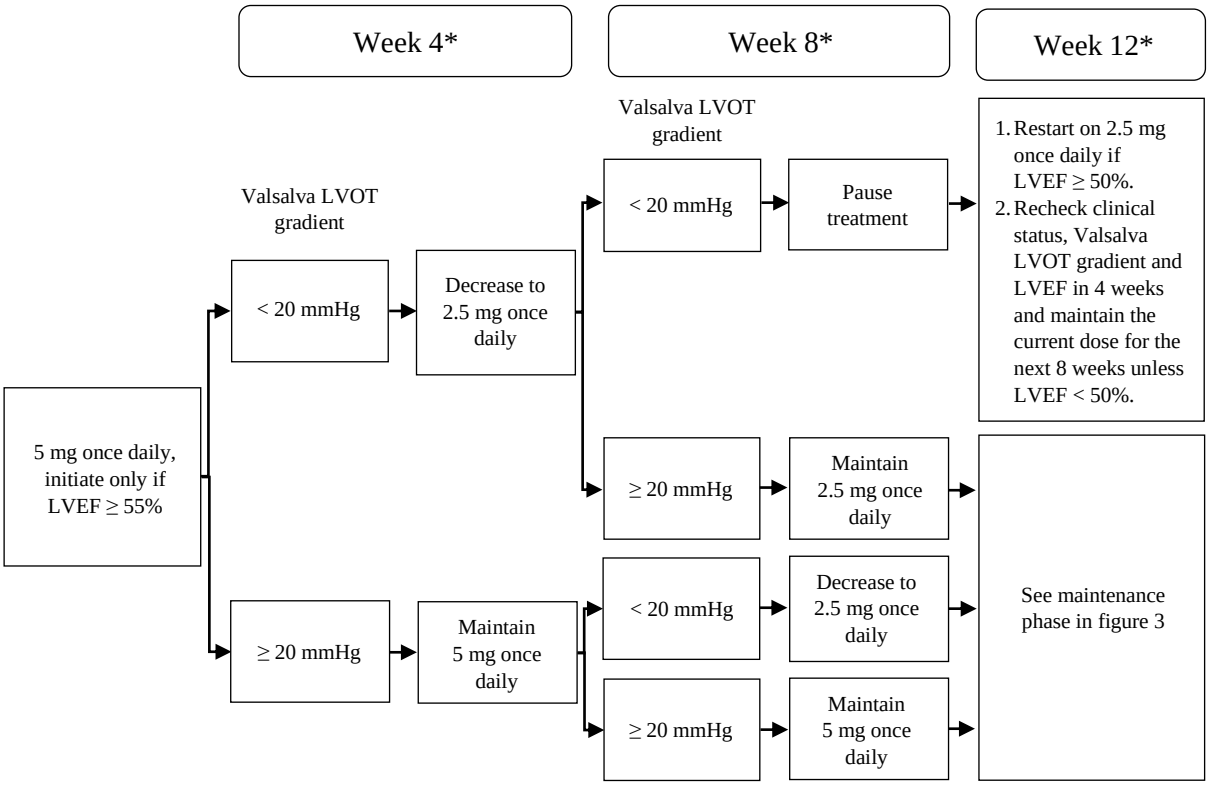
Consideration should be given to discontinue treatment in patients who have shown no response (e.g., no improvement in symptoms, quality of life, exercise capacity, LVOT gradient) after 4-6 months on the maximum tolerated dose.

Figure 1: Treatment initiation in CYP2C19 poor metaboliser phenotype



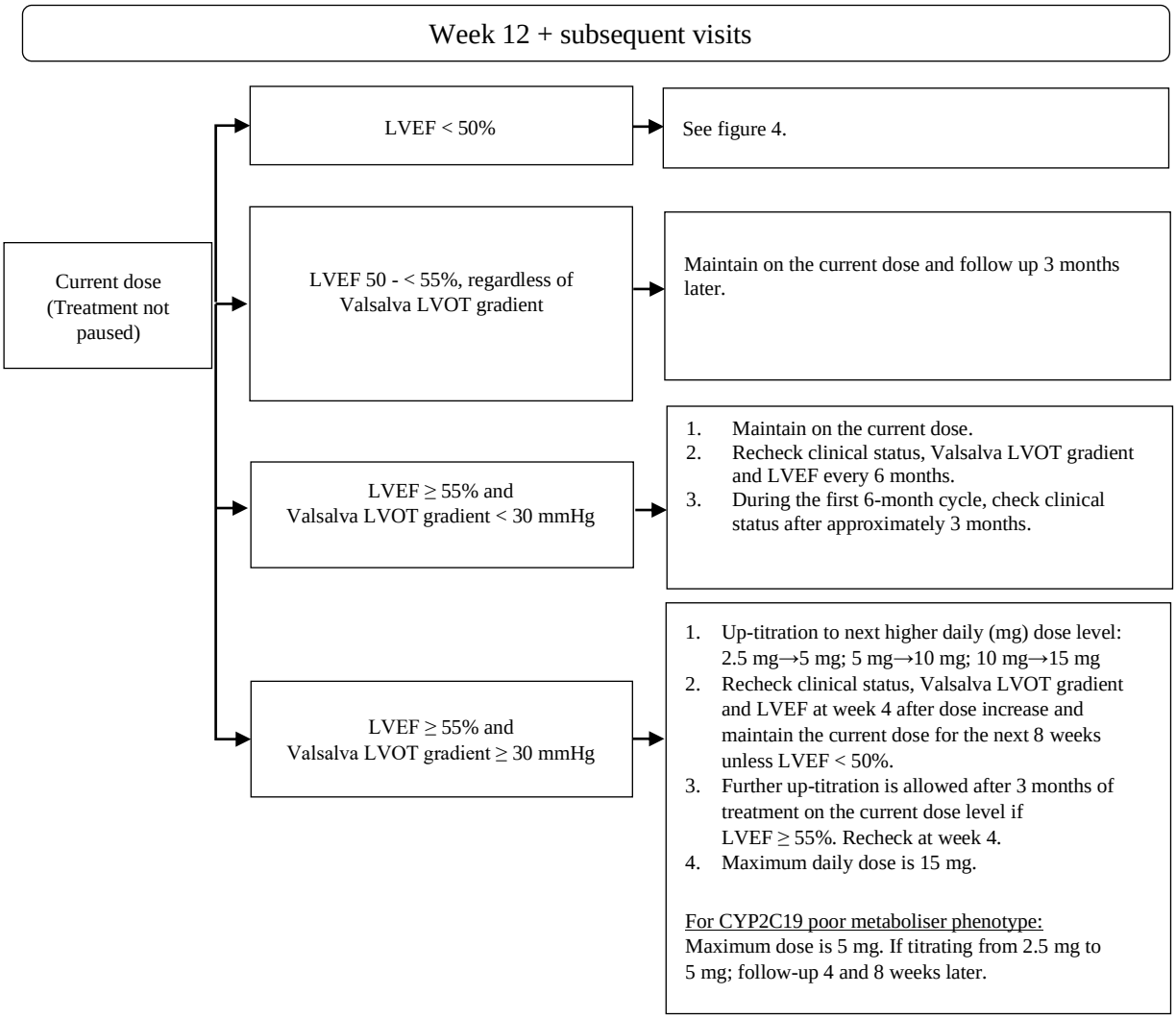
* Interrupt treatment if LVEF is < 50% at any clinical visit; restart treatment after 4 weeks if LVEF ≥ 50% (see figure 4).
LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

Figure 2: Treatment initiation in CYP2C19 intermediate, normal, rapid and ultra-rapid metaboliser phenotype



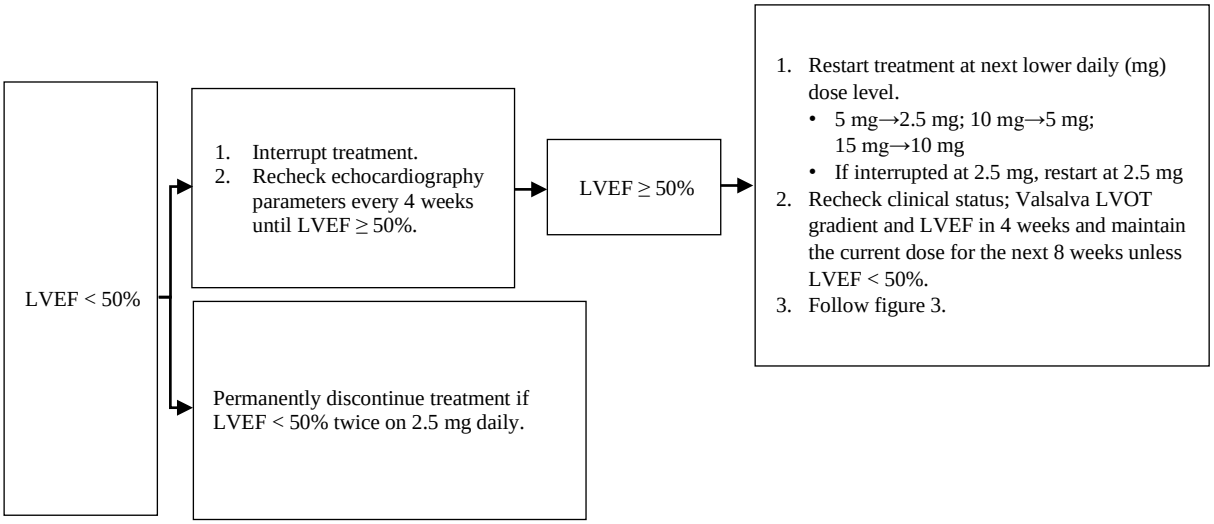
* Interrupt treatment if LVEF is < 50% at any clinical visit; restart treatment after 4 weeks if LVEF ≥ 50% (see figure 4).
LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

Figure 3: Maintenance phase



LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

Figure 4: Treatment interruption at any clinic visit if LVEF < 50%



LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

Dose modification with concomitant medicinal products
For concomitant treatment with inhibitors and inducers of CYP2C19 or CYP3A4, follow the steps shown in table 1 (see also section 4.5).

Table 1: Dose modification of mavacamten with concomitant medicinal products

Concomitant medicinal product	**CYP2C19 poor metaboliser phenotype***	**CYP2C19 intermediate, normal, rapid and ultra-rapid phenotype**
Inhibitors		
Combined use of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor	Contra-indicated (see section 4.3).	Contra-indicated (see section 4.3).
Strong CYP2C19 inhibitor	No dose adjustment (see section 4.5). **If CYP2C19 phenotype has not yet been determined:** No adjustment of the starting dose of 2.5 mg is needed. The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg (see section 4.5).	Initiate mavacamten at a dose of 2.5 mg. The dose should be reduced from 15 mg to 5 mg and from 10 mg and 5 mg to 2.5 mg or pause treatment if on 2.5 mg (see section 4.5).
Strong CYP3A4 inhibitor	Contra-indicated (see section 4.3).	No dose adjustment (see section 4.5).
Moderate CYP2C19 inhibitor	No dose adjustment. **If CYP2C19 phenotype has not yet been determined:** No adjustment of the starting dose of 2.5 mg is needed. The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg (see section 4.5).	No adjustment of the starting dose of 5 mg is needed. The dose should be reduced by one dose level or pause treatment if on 2.5 mg (see section 4.5).
Moderate or weak CYP3A4 inhibitor	No adjustment of the starting dose of 2.5 mg is needed. If patients are receiving a 5 mg dose of mavacamten, their dose should be reduced to 2.5 mg (see section 4.5).	No dose adjustment (see section 4.5).
Inducers		
Discontinuing or decreasing the dose of strong CYP2C19 inducer and strong CYP3A4 inducer	The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg (see section 4.5).	The dose should be reduced by one dose level when on doses 5 mg or higher when discontinuing or decreasing the dose of strong inducers while on mavacamten (see section 4.5). No dose adjustment when on 2.5 mg.
Discontinuing or decreasing the dose of moderate or weak CYP3A4 inducer	Decrease mavacamten dose to 2.5 mg or pause treatment if on 2.5 mg (see section 4.5).	No dose adjustment (see section 4.5).

* includes patients for whom the CYP2C19 phenotype has not yet been determined.

Missed or delayed doses
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. Two doses should not be taken on the same day.

Special populations

Elderly
No dose adjustment to the standard dose and titration scheme is required for patients aged 65 years and older (see section 5.2).

Renal impairment
No dose adjustment to the standard dose and titration scheme is required for patients with mild (estimated glomerular filtration rate [eGFR] 60-89 mL/min/1.73m^2) to moderate (eGFR 30-59 mL/min/1.73m^2) renal impairment. No dose recommendation can be made for patients with severe (eGFR < 30 mL/min/1.73m^2) renal impairment because mavacamten has not been studied in patients with severe renal impairment (see section 5.2).

Hepatic impairment
The mavacamten starting dose should be 2.5 mg in all patients with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment since mavacamten exposure is likely to be increased (see section 5.2). No dose recommendation can be made for patients with severe hepatic impairment (Child-Pugh class C) because mavacamten has not been studied in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of mavacamten in children and adolescents below 18 years have not been established. No data are available.
Mavacamten should not be used in children less than 12 years because of potential safety concerns.

Method of administration

For oral use.

Treatment should be taken once daily with or without meals at about the same time each day. The capsule should be swallowed whole with water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- During pregnancy and in women of childbearing potential not using effective contraception (see sections 4.4 and 4.6).
- Concomitant treatment with strong CYP3A4 inhibitors in patients with CYP2C19 poor metaboliser phenotype and undetermined CYP2C19 phenotype (see sections 4.2, 4.4 and 4.5).
- Concomitant treatment with the combination of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor (see section 4.5).

4.4 Special warnings and precautions for use

Systolic dysfunction defined as symptomatic LVEF < 50%

Mavacamten reduces LVEF and may cause heart failure due to systolic dysfunction defined as symptomatic LVEF < 50%. Patients with a serious intercurrent illness such as infection or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia), or those undergoing major cardiac surgery may be at greater risk of systolic dysfunction and progress to heart failure (see section 4.8). New or worsening dyspnoea, chest pain, fatigue, palpitations, leg oedema or elevations in N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be signs and symptoms of systolic dysfunction and should prompt an evaluation of cardiac function. LVEF should be measured prior to initiating treatment and closely monitored thereafter. Treatment interruption may be necessary to ensure that LVEF remains ≥ 50% (see section 4.2).

Heart failure risk or loss of response to mavacamten due to interactions

Mavacamten is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4 and mostly by CYP3A4 in CYP2C19 poor metabolisers, which may lead to the following interactions (see section 4.5):

- Starting or increasing the dose of a strong or moderate CYP3A4 inhibitor or any CYP2C19 inhibitor may increase risk of heart failure due to systolic dysfunction.
- Stopping or decreasing dose of any inhibitor of CYP3A4 or CYP2C19 may lead to a loss of therapeutic response to mavacamten.
- Starting a strong CYP3A4 or strong CYP2C19 inducer may lead to a loss of therapeutic response to mavacamten.
- Stopping a strong CYP3A4 or strong CYP2C19 inducer may increase risk of heart failure due to systolic dysfunction.

Prior to and during mavacamten treatment, the potential for interactions, including over the counter medicinal products (such as omeprazole or esomeprazole), should be considered.

- Concomitant treatment with strong CYP3A4 inhibitors in patients with CYP2C19 poor metaboliser phenotype and undetermined CYP2C19 phenotype is contraindicated (see section 4.3).
- Concomitant treatment with the combination of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor is contraindicated (see section 4.3)
- Dose adjustment of mavacamten and/or close monitoring may be required in patients initiating or discontinuing treatment with, or changing the dose of concomitant medicinal products that are inhibitors or inducers of CYP2C19 or CYP3A4 (see sections 4.2 and 4.5). Intermittent administration of these medicinal products is not recommended (see section 4.5).

Concomitant use of negative inotropes

The safety of concomitant use of mavacamten with disopyramide, or use of mavacamten in patients taking beta blockers in combination with verapamil or diltiazem has not been established. Therefore, patients should be closely monitored when taking these concomitant medicinal products (see section 4.5).

Embryo-foetal toxicity

Based on animal studies, mavacamten is suspected to cause embryo-foetal toxicity when administered to a pregnant woman (see section 5.3). Due to risk to the foetus, CAMZYOS is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for 6 months after treatment discontinuation (see sections 4.3 and 4.6).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

If treatment with a new negative inotrope is initiated or if the dose of a negative inotrope is increased in a patient receiving mavacamten, close medical supervision with monitoring of LVEF should be provided until stable doses and clinical response have been achieved (see sections 4.2 and 4.4).

Pharmacokinetic interactions

Effect of other medicinal products on mavacamten
In CYP2C19 intermediate, normal, rapid and ultra-rapid metabolisers, mavacamten is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4. In CYP2C19 poor metabolisers, metabolism is mostly by CYP3A4 (see section 5.2). CYP2C19 inhibitors/inducers and CYP3A4 inhibitors/inducers may thus affect the clearance of mavacamten and increase/decrease mavacamten plasma concentration, and this will depend on the CYP2C19 phenotype.
All clinical drug-drug interaction studies mainly enrolled CYP2C19 normal metabolisers and no CYP2C19 poor metabolisers were included in the assessment of the drug-drug interaction and therefore the effect of co-administration of CYP2C19 and CYP3A4 inhibitors with mavacamten in CYP2C19 poor metabolisers is not completely certain.
Recommendations for dose modification and/or additional monitoring of patients initiating or discontinuing treatment with, or changing the dose of, concomitant medicinal products that are inhibitors of CYP2C19 or CYP3A4 or inducers of CYP2C19 or CYP3A4 are provided in table 2.

Strong CYP2C19 plus strong CYP3A4 inhibitors
Co-administration of mavacamten with the combination of a strong CYP2C19 and a strong CYP3A4 inhibitor is contra-indicated (see section 4.3).

CYP2C19 inhibitors
The effect of a moderate and strong CYP2C19 inhibitor on the PK of mavacamten was not investigated in a clinical drug-drug interaction study. The effect of a strong CYP2C19 inhibitor (e.g., ticlopidine) will be similar to the effect of the CYP2C19 poor metabolising status (see table 1).
Co-administration of mavacamten with a weak CYP2C19 inhibitor (omeprazole) resulted in a 48% increase in mavacamten AUC_{inf} with no effect on C_{max} in CYP2C19 normal metabolisers.
Intermittent administration of a CYP2C19 inhibitor (such as omeprazole or esomeprazole) is not recommended (see section 4.4).

CYP3A4 inhibitors
The effect of strong CYP3A4 inhibitors on the PK of mavacamten was not investigated in a clinical drug-drug interaction study. Co-administration of mavacamten with a strong CYP3A4 inhibitor (itraconazole) in CYP2C19 normal metabolisers is expected to result in an increase in mavacamten plasma concentration of up to 59% and 40% in AUC_{0-24} and C_{max}, respectively.
Co-administration of mavacamten with a moderate CYP3A4 inhibitor (verapamil) in CYP2C19 normal metabolisers resulted in an increase in mavacamten plasma concentration of 16% and 52% in AUC_{inf} and C_{max}, respectively. This change was not considered clinically significant.

CYP2C19 and CYP3A4 inducers
No clinical interaction studies were conducted to investigate the effect of concomitant administration with a strong CYP3A4 and CYP2C19 inducer. Co-administration of mavacamten with a strong inducer of both CYP2C19 and CYP3A4 (e.g., rifampicin) is expected to significantly affect the pharmacokinetics (PK) of mavacamten and leads to reduced efficacy and therefore co-administration with strong inducers of both CYP2C19 and CYP3A4 is not recommended. If discontinuing concomitant treatment with a strong inducer of CYP2C19 or CYP3A4 increase clinical assessments and mavacamten dose should be reduced (see section 4.2).

Table 2: Dose modification/monitoring of mavacamten with concomitant medicinal products

Concomitant medicinal product	**CYP2C19 poor metaboliser phenotype***	**CYP2C19 intermediate, normal, rapid and ultra-rapid metaboliser phenotype**
Inhibitors		
Combined use of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor	Contra-indicated (see section 4.3)	Contra-indicated (see section 4.3)
Strong CYP2C19 inhibitor (e.g., ticlopidine, fluconazole, fluvoxamine)	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2). **If CYP2C19 phenotype has not yet been determined:** No adjustment of the starting dose of 2.5 mg is needed. The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2).	Initiate mavacamten at a dose of 2.5 mg. The dose should be reduced from 15 mg to 5 mg and from 10 mg and 5 mg to 2.5 mg or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2).
Strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole, ketoconazole, voriconazole, ritonavir, cobicistat, ceritinib, idelalisib, tucatinib)	Contra-indicated (see section 4.3)	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2).
Moderate CYP2C19 inhibitor (e.g., fluconazole, fluoxetine, omeprazole[a])	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment (see section 4.2). **If CYP2C19 phenotype has not yet been determined:** No adjustment of the starting dose of 2.5 mg is needed. The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment (see section 4.2).	No adjustment of the starting dose of 5 mg is needed. *Initiating or increasing the dose of a moderate inhibitor while on mavacamten treatment:* Dose should be reduced by one dose level or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2).
Moderate CYP3A4 inhibitor (e.g., erythromycin, grapefruit juice, verapamil, diltiazem)	If on medication when starting mavacamten, no adjustment of the starting dose of 2.5 mg is needed. *Initiating or increasing the dose of a moderate inhibitor while on mavacamten treatment:* If patients are receiving a 5 mg dose of mavacamten, their dose should be reduced to 2.5 mg or if on 2.5 mg pause treatment for 4 weeks. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2).	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2).

Concomitant medicinal product	**CYP2C19 poor metaboliser phenotype***	**CYP2C19 intermediate, normal, rapid and ultra-rapid metaboliser phenotype**
Weak CYP2C19 inhibitor (e.g., cimetidine, citalopram, omeprazole[a], esomeprazole)	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment (see section 4.2).	*Initiating or increasing the dose of a weak inhibitor while on mavacamten treatment:* Monitor LVEF 4 weeks later, and subsequently resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment (see section 4.2).
Weak CYP3A4 inhibitor (e.g., cimetidine, esomeprazole, omeprazole, pantoprazole)	If on medication when starting mavacamten, no adjustment of the starting dose of 2.5 mg is needed. *Initiating or increasing the dose of weak inhibitor while on mavacamten treatment:* If patients are receiving a 5 mg dose of mavacamten, their dose should be reduced to 2.5 mg or if on 2.5 mg pause treatment for 4 weeks. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2).	*Initiating or increasing the dose of a weak inhibitor while on mavacamten treatment:* No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment (see section 4.2).
Inducers		
Strong CYP2C19 inducer and strong CYP3A4 inducer (e.g., rifampicin, apalutamide, enzalutamide, mitotane, phenytoin, carbamazepine, efavirenz, St. John's wort)	*Initiating or increasing the dose of strong inducer while on mavacamten treatment:* Monitor LVOT gradient and LVEF 4 weeks later. Adjust mavacamten dose based on clinical assessment and then resume the patient's monitoring and titration schedule (see section 4.2). The maximum dose is 5 mg. *Discontinuing or decreasing the dose of strong inducer while on mavacamten treatment:* Decrease mavacamten dose from 5 mg to 2.5 mg or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2).	*Initiating or increasing the dose of strong inducer while on mavacamten treatment:* Monitor LVOT gradient and LVEF 4 weeks later. Adjust mavacamten dose based on clinical assessment and then resume the patient's monitoring and titration schedule (see section 4.2). *Discontinuing or decreasing the dose of strong inducer while on mavacamten treatment:* Decrease mavacamten by one dose level when on doses 5 mg or higher. Maintain mavacamten dose when on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2).

Concomitant medicinal product	**CYP2C19 poor metaboliser phenotype***	**CYP2C19 intermediate, normal, rapid and ultra-rapid metaboliser phenotype**
Moderate or weak CYP2C19 inducer (e.g., letermovir, norethindrone, prednisone)	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment (see section 4.2).	*Initiating the dose of moderate or weak inducer while on mavacamten treatment:* Monitor LVOT gradient and LVEF 4 weeks later. Adjust mavacamten dose based on clinical assessment and then resume the patient's monitoring and titration schedule (see section 4.2). *Discontinuing a moderate or weak inducer while on mavacamten treatment:* Decrease mavacamten by one dose level when on doses 5 mg or higher. Maintain mavacamten dose when on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment (see section 4.2).
Moderate or weak CYP3A4 inducer (e.g., phenobarbital, primidone)	*Initiating or increasing the dose of moderate or weak inducer while on mavacamten treatment:* Monitor LVOT gradient and LVEF 4 weeks later. Adjust mavacamten dose based on clinical assessment and then resume the patient's monitoring and titration schedule (see section 4.2). *Discontinuing or decreasing the dose of moderate or weak inducer while on mavacamten treatment:* Decrease mavacamten dose to 2.5 mg or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule (see section 4.2).	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment (see section 4.2).

* Includes patients for whom the CYP2C19 phenotype has not yet been determined.
[a] Omeprazole is considered a weak CYP2C19 inhibitor at a dose of 20 mg once daily and a moderate CYP2C19 inhibitor at a total daily dose of 40 mg.

Effect of mavacamten on other medicinal products

Mavacamten *in vitro* data suggest a potential induction of CYP3A4. Co-administration of a 17-day course of mavacamten at clinical relevant exposures in CYP2C19 normal, rapid and ultra-rapid metabolisers did not decrease the exposure to ethinyl oestradiol and norethindrone, which are the components of typical oral contraceptives and substrates for CYP3A4. Furthermore, co-administration of a 16-day course of mavacamten in CYP2C19 normal metabolisers, at clinical relevant exposures, resulted in a 13% decrease in midazolam plasma concentration. This change was not considered clinically significant.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females

CAMZYOS is contraindicated in women of childbearing potential not using effective contraception (see section 4.3). Therefore, before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available and counselling should be provided regarding the serious risk to the foetus. Women of childbearing potential must use effective contraception during treatment and for 6 months after discontinuation of CAMZYOS, since it takes approximately 5 half-lives (approximately 45 days for CYP2C19 normal metabolisers and 115 days for CYP2C19 poor metabolisers) to eliminate mavacamten from the body after treatment discontinuation (see sections 4.4 and 5.2).

When stopping mavacamten therapy for planning a pregnancy the possible return of LVOT obstruction and symptom burden should be considered (see section 4.4).

Pregnancy

There are no data from the use of mavacamten in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Mavacamten is suspected to cause embryo-foetal toxicity when administered during pregnancy. Therefore, CAMZYOS is contraindicated during pregnancy (see section 4.3). CAMZYOS should be stopped 6 months before planning a pregnancy (see section 4.4). If a patient becomes pregnant, mavacamten must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment and ultrasonography examinations should be performed.

Breast-feeding

It is unknown whether mavacamten or its metabolites are excreted in human milk. There is no information on the excretion of mavacamten or its metabolites in animal milk (see section 5.3). Because of the unknown adverse effects of mavacamten in breastfed newborns/infants, women must not breast-feed during treatment with mavacamten.

Fertility

No human fertility data on mavacamten are available. Studies in animals are insufficient with respect to male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Mavacamten has minor influence on the ability to drive and use machines. Dizziness may occur during use of mavacamten. Patients should be advised not to drive or use machines if they experience dizziness.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions with mavacamten are dizziness (17%), dyspnoea (12%), systolic dysfunction (5%) and syncope (5%).

Tabulated list of adverse reactions

Adverse reactions reported in patients treated with mavacamten in two phase 3 studies (EXPLORER-HCM and VALOR-HCM) are tabulated below. A total of 179 patients received a daily dose of either 2.5 mg, 5 mg, 10 mg or 15 mg of mavacamten. The median treatment duration for patients receiving mavacamten was 30.1 weeks (range: 1.6 to 40.3 weeks).

The adverse reactions included in table 3 are listed according to system organ class in MedDRA. Within each system organ class, the adverse reactions are presented in order of decreasing frequency and seriousness. In addition, the corresponding frequency category for each adverse reaction is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Table 3: Adverse reactions

System organ class	Adverse reaction	Frequency
Nervous system disorders	Dizziness	Very common
	Syncope	Common
Cardiac disorders	Systolic dysfunction[a]	Common
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common

[a] Defined as LVEF < 50% with or without symptoms.

Description of selected adverse reactions

Systolic dysfunction
In Phase 3 clinical studies, 5% (9/179) of patients in the mavacamten group experienced reversible reductions in LVEF < 50% (median 45%: range: 35-49%) while on treatment. In 56% (5/9) of these patients, reductions were observed without other clinical manifestations. In all patients treated with mavacamten, LVEF recovered following interruption of mavacamten and they completed the study on treatment (see section 4.4).

Dyspnoea
In Phase 3 clinical studies, dyspnoea was reported in 12.3% of patients treated with mavacamten compared to 8.7% of patients on placebo. In the EXPLORER-HCM study, most (67%) of the dyspnoea events were reported after mavacamten was discontinued, with median time to onset of 2 weeks (range: 0.1-4.9) after last dose.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience of overdose with mavacamten is limited. Mavacamten has been given as a single dose of up to 144 mg in patients with HCM. There was one serious adverse reaction of vasovagal reaction, hypotension, and asystole lasting 38 seconds reported at that dose. In healthy subjects, doses of up to 25 mg have been administered for up to 25 days. A reduction of LVEF by 20% or greater was experienced in 3 out of 8 participants treated at the 25 mg dose level. Systolic dysfunction is the most likely result of overdose of mavacamten. If warranted, treatment of overdose with mavacamten consists of discontinuation of mavacamten treatment as well as medically supportive measures to maintain hemodynamic status (e.g. initiation of inotropic support with adrenergic agents), including close monitoring of vital signs and LVEF and management of the clinical status of the patient.

In healthy subjects fasted overnight, administration of activated charcoal 2 hours (approximately t_{max}) after ingestion of a 15 mg dose of mavacamten reduced absorption as expressed by $AUC_{0\ 72}$ by 20%. Administration of activated charcoal 6 hours after the mavacamten dose had no effect on the absorption. Thus, early administration (prior to or as soon after t_{max} as possible) of activated charcoal may be considered in the management of mavacamten overdose or accidental ingestion. Under fed

conditions, activated charcoal may still be effective beyond 2 hour post mavacamten dose because of the delayed t_{max} (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, Other cardiac preparations, ATC code: C01EB24

Mechanism of action

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.

Pharmacodynamic effects

LVEF
In the EXPLORER-HCM study, mean (SD) resting LVEF was 74% (6) at baseline in both treatment arms, reductions in mean absolute change from baseline in LVEF was -4% (95% CI: -5.3, -2.5) in the mavacamten arm and 0% (95% CI: -1.2, 1.0) in the placebo arm over the 30-week treatment period. At Week 38, following an 8-week interruption of mavacamten, mean LVEF was similar to baseline for both treatment arms.

LVOT obstruction
In the EXPLORER-HCM study, patients achieved reductions in mean resting and provoked (Valsalva) LVOT gradient by week 4 which were sustained throughout the 30-week study duration. At week 30, the mean change from baseline in resting and Valsalva LVOT gradients were -39 (95% CI: -44.0, -33.2) mmHg and -49 (95% CI: -55.4, -43.0) mmHg, respectively, for mavacamten arm and -6 (95% CI: -10.5, -0.5) mmHg and -12 (95% CI: -17.6, -6.6) mmHg, respectively, for the placebo arm. At week 38, following 8 weeks of mavacamten washout, mean LVEF and LVOT gradients were similar to baseline for both treatment arms.

Cardiac electrophysiology
In HCM, the QT interval may be intrinsically prolonged due to the underlying disease, in association with ventricular pacing, or in association with medicinal products with potential for QT prolongation commonly used in the HCM population. An exposure-response analysis across all clinical studies in HCM patients has shown a concentration-dependent shortening of the QTcF interval with mavacamten. The mean placebo corrected change from baseline in oHCM patients was -8.7 ms (upper and lower limit of the 90% CI -6.7 ms and -10.8 ms, respectively) at the median steady-state C_{max} of 452 ng/mL. Patients with longer baseline QTcF intervals tended to display the greatest shortening.

Consistent with nonclinical findings in normal hearts, in one clinical study in healthy subjects sustained exposure to mavacamten at supratherapeutic levels leading to marked depression of systolic function was associated with QTc prolongation (< 20 ms). No acute QTc changes have been observed at comparable (or higher) exposures after single doses. The findings in healthy hearts are attributed to an adaptive response to the cardiac mechanical/functional changes (marked mechanical LV depression) occurring in response to myosin inhibition in hearts with normal physiology and LV contractility.

Clinical efficacy and safety

EXPLORER-HCM

The efficacy of mavacamten was evaluated in a double-blind, randomised, placebo-controlled, parallel-arm, multicentre, international, Phase 3 study enrolling 251 adult patients with NYHA class II and III oHCM, LVEF ≥ 55%, and LVOT peak gradient ≥ 50 mmHg at rest or with provocation at time of oHCM diagnosis and Valsalva LVOT gradient ≥ 30 mmHg at screening. The majority of patients received background HCM treatment for a total of 96% in mavacamten arm (beta blockers 76%, calcium channel blockers 20%) and of 87% in the placebo arm (beta blockers 74%, calcium channel blockers 13%).

Patients were randomised in a 1:1 ratio to receive either a starting dose of 5 mg of mavacamten (123 patients) or matching placebo (128 patients) once daily for 30 weeks. The dose was periodically adjusted to optimise patients' response (decrease in LVOT gradient with Valsalva manoeuvre), maintain LVEF ≥ 50%, and was also guided by plasma concentrations of mavacamten. Within the dose range of 2.5 mg to 15 mg, a total of 60 patients received 5 mg and 40 patients received 10 mg. During the study, 3 of 7 patients on mavacamten had LVEF < 50% prior to the week 30 visit and temporarily interrupted their dose; 2 patients resumed treatment at the same dose and 1 patient had the dose reduced from 10 mg to 5 mg.

Treatment assignment was stratified by baseline NYHA class (II or III), current treatment with beta blockers (yes or no), and type of ergometer (treadmill or exercise bicycle) used for assessment of peak oxygen consumption (pVO_2). Patients on background dual treatment with beta blocker and calcium channel blocker treatment or disopyramide or ranolazine were excluded. Patients with known infiltrative or storage disorder causing cardiac hypertrophy that mimicked oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy, were also excluded.

The baseline demographic and disease characteristics were balanced between mavacamten and placebo. The mean age was 59 years, 54% (mavacamten) *vs* 65% (placebo) were male, mean body mass index (BMI) was 30 kg/m^2, mean heart rate 63 bpm, mean blood pressure 128/76 mmHg, and 90% were Caucasian. At baseline, approximately 73% of randomised subjects were NYHA class II and 27% were NYHA class III. The mean LVEF was 74%, and the mean Valsalva LVOT was 73 mmHg. 8% had prior septal reduction therapy, 75% were on beta -blockers, 17% were on calcium channel blockers, 14% had history of atrial fibrillation, and 23% with implantable cardioverter defibrillator (23%). In EXPLORER-HCM there were 85 patients aged 65 years or older, 45 patients were dosed with mavacamten.

The primary outcome measure included a change at week 30 in exercise capacity measured by pVO_2 and symptoms measured by NYHA functional classification, defined as an improvement of pVO_2 by ≥ 1.5 mL/kg/min and an improvement in NYHA class by at least 1 OR an improvement of pVO_2 by ≥ 3.0 mL/kg/min and no worsening in NYHA class.

A greater proportion of patients treated with mavacamten met the primary and secondary endpoints at week 30 compared to placebo (see table 4).

Table 4: Analysis of the primary composite and secondary endpoints from EXPLORER-HCM study

	Mavacamten N = 123	**Placebo N = 128**
Patients achieving primary endpoint at week 30, n (%)	45 (37%)	22 (17%)
Treatment difference (95% CI)	19.4 (8.67, 30.13)	
p-value	0.0005	

	Mavacamten N = 123	**Placebo N = 128**
Change from baseline post-exercise LVOT peak gradient at week 30, mmHg	N = 123	N = 128
Mean (SD)	-47 (40)	-10 (30)
Treatment difference* (95% CI)	-35 (-43, -28)	
p-value	< 0.0001	
Change from baseline to week 30 in pVO_2, mL/kg/min	N = 123	N = 128
Mean (SD)	1.4 (3)	-0.05 (3)
Treatment difference* (95% CI)	1.4 (0.6, 2)	
p-value	< 0.0006	
Patients with improvement of NYHA class ≥ 1 at week 30	N = 123	N = 128
N, (%)	80 (65%)	40 (31%)
Treatment difference (95% CI)	34 (22, 45)	
p-value	< 0.0001	
Change from baseline to week 30 in KCCQ-23 CSS†	N = 92	N = 88
Mean (SD)	14 (14)	4 (14)
Treatment difference* (95% CI)	9 (5, 13)	
p-value	< 0.0001	
Baseline	N = 99	N = 97
Mean (SD)	71 (16)	71 (19)
Change from baseline to week 30 in HCMSQ SoB domain score‡	N = 85	N = 86
Mean (SD)	-2.8 (2.7)	-0.9 (2.4)
Treatment difference* (95% CI)	-1.8 (-2.4, -1.2)	
p-value	< 0.0001	
Baseline	N = 108	N = 109
Mean (SD)	4.9 (2.5)	4.5 (3.2)

* Least-squares mean difference
† KCCQ-23 CSS = Kansas City Cardiomyopathy Questionnaire-23 Clinical Summary Score. The KCCQ-23 CSS is derived from the Total Symptoms Score (TSS) and the Physical Limitations (PL) score of the KCCQ-23. The CSS ranges from 0 to 100, with higher scores representing better health status. A significant treatment effect on the KCCQ-23 CSS favouring mavacamten was first observed at week 6 and remained consistent through week 30.
‡ HCMSQ SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath. The HCMSQ SoB domain score measures frequency and severity of shortness of breath. The HCMSQ SoB domain score ranges from 0 to 18, with lower scores representing less shortness of breath. A significant treatment effect on the HCMSQ SoB favouring mavacamten was first observed at week 4 and remained consistent through week 30.

A range of demographic characteristics, baseline disease characteristics, and baseline concomitant medicinal products were examined for their influence on outcomes. Results of the primary analysis consistently favoured mavacamten across all subgroups analysed.

VALOR-HCM
The efficacy of mavacamten was evaluated in a Phase 3, double-blind, randomised, 16-week placebo-controlled trial in 112 patients with symptomatic oHCM who were septal reduction therapy (SRT) eligible. Patients with severely symptomatic drug-refractory oHCM, and NYHA class III/IV or class II with exertional syncope or near syncope were included in the study. Patients were required to have LVOT peak gradient ≥ 50 mmHg at rest or with provocation, and LVEF ≥ 60%. Patients must have been referred or under active consideration within the past 12 months for SRT and had been actively considering scheduling the procedure.

Patients were randomised 1:1 to receive treatment with mavacamten or placebo once daily. The dose was periodically adjusted within the dose range of 2.5 mg to 15 mg to optimise patient's response.

The baseline demographic and disease characteristics were balanced between mavacamten and placebo. The mean age was 60.3 years, 51% were male, mean BMI was 31 kg/m^2, mean heart rate 64 bpm, mean blood pressure 131/74 mmHg, and 89% were Caucasian. At baseline, approximately 7% of randomised subjects were NYHA class II and 92% were NYHA class III. 46% were on beta-blockers monotherapy, 15% were on calcium channel blockers monotherapy, 33% were on a mixed combination of beta -blockers, calcium channel blockers, and 20% were on disopyramide alone or in combination with other treatment. In VALOR-HCM there were 45 patients aged 65 years or older, 24 patients were dosed with mavacamten.

Mavacamten was shown to be superior to placebo in meeting the primary composite endpoint at week 16 (see table 5). The primary endpoint was a composite of

- patient decision to proceed with SRT prior to or at week 16 or
- patients who remain SRT eligible (LVOT gradient of ≥ 50 mmHg and NYHA class III-IV, or class II with exertional syncope or near syncope) at week 16.

The treatment effects of mavacamten on LVOT obstruction, functional capacity, health status, and cardiac biomarkers were assessed by change from baseline through week 16 in post-exercise LVOT gradient, proportion of patients with improvement in NYHA class, KCCQ-23 CSS, NT-proBNP, and cardiac troponin I. In the VALOR-HCM study, hierarchical testing of secondary efficacy endpoints showed significant improvement in the mavacamten group compared to the placebo group (see table 5).

Table 5: Analysis of the primary composite and secondary endpoints from VALOR-HCM study

	Mavacamten N = 56	**Placebo N = 56**
Patients achieving primary composite endpoint at week 16, n (%)	10 (17.9)	43 (76.8)
Treatment difference (95% CI)	58.9 (44.0, 73.9)	
p-value	< 0.0001	
Patient decision to proceed with SRT	2 (3.6)	2 (3.6)
SRT-eligible based on guideline criteria	8 (14.3)	39 (69.6)
SRT status not evaluable (imputed as meeting primary endpoint)	0 (0.0)	2 (3.6)
Change from baseline post-Exercise LVOT peak gradient at week 16, (mmHg)	N = 55	N = 53
Mean (SD)	-39.1 (36.5)	-1.8 (28.8)
Treatment difference* (95% CI)	-37.2 (-48.1, -26.2)	
p-value	< 0.0001	
Patients with improvement of NYHA class ⩾ 1 at week 16	N = 55	N = 53
N, (%)	35 (62.5%)	12 (21.4%)
Treatment difference (95% CI)	41.1 (24.5%, 57.7%)	
p-value	< 0.0001	
Change from baseline to week 16 in KCCQ-23 CSS†	N = 55	N = 53
Mean (SD)	10.4 (16.1)	1.8 (12.0)
Treatment difference* (95% CI)	9.5 (4.9, 14.0)	
p-value	< 0.0001	
Baseline	N = 56	N = 56
mean (SD)	69.5 (16.3)	65.6 (19.9)

	Mavacamten N = 56	**Placebo N = 56**
Change from baseline to week 16 in NT-proBNP	N = 55	N = 53
ng/L geometric mean ratio	0.35	1.13
Geometric mean ratio mavacamten/placebo (95% CI)	0.33 (0.27, 0.42)	
p-value	< 0.0001	
Change from baseline to week 16 in Cardiac Troponin I	N = 55	N = 53
ng/L geometric mean ratio	0.50	1.03
Geometric mean ratio mavacamten/placebo (95% CI)	0.53 (0.41, 0.70)	
p-value	< 0.0001	

* Least-squares mean difference.
† KCCQ-23 CSS=Kansas City Cardiomyopathy Questionnaire-23 Clinical Summary Score. The KCCQ-23 CSS is derived from the Total Symptoms Score (TSS) and the Physical Limitations (PL) score of the KCCQ-23. The CSS ranges from 0 to 100, with higher scores representing better health status.

In the VALOR-HCM study, secondary endpoint of NT-proBNP, at week 16 (see table 5) showed a sustained reduction from baseline after mavacamten treatment compared to placebo that was similar to that seen in EXPLORER-HCM at week 30.
Exploratory analysis of left ventricular mass index (LVMI) and left atrial volume index (LAVI) showed reductions in the mavacamten treated patients compared to placebo in EXPLORER-HCM and VALOR-HCM.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with CAMZYOS in one or more subsets of the paediatric population in treatment of HCM (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Mavacamten is readily absorbed with a median t_{max} of 1 hour (range: 0.5 to 3 hours) after oral administration with an estimated oral bioavailability of approximately 85% within the clinical dose range. The increase in mavacamten exposure is generally dose proportional after once daily doses of mavacamten (2 mg to 48 mg).

After a single dose of 15 mg mavacamten, C_{max} and AUC_{inf} are 47% and 241% higher, respectively, in CYP2C19 poor metabolisers compared to normal metabolisers. Mean half-life is prolonged in CYP2C19 poor metabolisers compared to normal metabolisers (23 days *versus* 6 to 9 days, respectively).

Inter-subject PK variability is moderate, with a coefficient of variation for exposure of approximately 30-50% for C_{max} and AUC.

A high fat, high calorie meal delayed absorption resulting in a median t_{max} of 4 hours (range: 0.5 to 8 hours) in the fed state compared to 1 h in the fasted state. Administration with meals resulted in a 12% decrease in $AUC_{0\text{-}inf}$, however this decrease is not considered clinically significant. Mavacamten may be administered with or without meals.

As mavacamten is titrated based on clinical response (see section 4.2), simulated steady state exposures are summarized using individualised dosage by phenotype (see table 6).

Table 6: Simulated average steady state concentration by dose and CYP2C19 phenotype in patients titrated to effect based on Valsalva LVOT and LVEF

Dose	Median concentration (ng/mL)				
	Poor metabolisers	**Intermediate metabolisers**	**Normal metabolisers**	**Rapid metabolisers**	**Ultra-rapid metabolisers**
2.5 mg	451.9	274.0	204.9	211.3	188.3
5 mg	664.9	397.8	295.4	311.5	300.5

Distribution

Plasma protein binding of mavacamten is 97-98% in clinical studies. The blood-to-plasma concentration ratio is 0.79. The apparent volume of distribution (Vd/F) ranged from 114 L to 206 L. Specific studies to assess distribution of mavacamten have not been conducted in humans, however data are consistent with a high volume of distribution.

Based upon 10 male subjects dosed for up to 28 days, the amount of mavacamten distributed to the semen was considered to be low.

Biotransformation

Mavacamten is extensively metabolised, primarily through CYP2C19 (74%), CYP3A4 (18%), and CYP2C9 (7.6%) based on in-vitro reaction phenotyping. Metabolism is expected to be driven through all three pathways, and primarily through CYP2C19 in CYP2C19 intermediate, normal, rapid and ultra-rapid metabolisers. Three metabolites have been detected in human plasma. The exposure of the most abundant metabolite MYK-1078 in human plasma was less than 4% of the exposure of mavacamten, and the other two metabolites had exposures less than 3% of the exposure of mavacamten indicating these would have minimal to no impact on the overall activity of mavacamten. In CYP2C19 poor metabolisers mavacamten is metabolised primarily by CYP3A4. No data are available on the metabolite profile in CYP2C19 poor metabolisers.

Effect of mavacamten on other CYP enzymes
Based on pre-clinical data, for a dose up to 5 mg in CYP2C19 poor metabolisers and for a dose up to 15 mg in CYP2C19 intermediate to ultra-rapid metabolisers, mavacamten is not an inhibitor of CYP 1A2, 2B6, 2C8, 2D6, 2C9, 2C19, or 3A4 at clinically relevant concentrations.

Effect of mavacamten on transporters
In vitro data indicate that mavacamten is not an inhibitor of major efflux transporters (P-gp, BCRP, BSEP, MATE1, or MATE2-K) or major uptake transporters (organic anion transporting polypeptides [OATPs], organic cation transporters [OCTs], or organic anion transporters [OATs]) at therapeutic concentrations for a dose up to 5 mg in CYP2C19 poor metabolisers and for a dose up to 15 mg in CYP2C19 intermediate to ultra-rapid metabolisers.

Elimination

Mavacamten is cleared from plasma primarily by metabolism through cytochrome P450 enzymes. Terminal half-life is 6 to 9 days in CYP2C19 normal metabolisers and 23 days for CYP2C19 poor metabolisers.
Half-life is estimated to be, 6 days for CYP2C19 ultra-rapid metabolisers, 8 days for CYP2C19 rapid metabolisers, and 10 days for CYP2C19 intermediate metabolisers.

Drug accumulation occurs with an accumulation ratio about 2-fold for C_{max} and about 7-fold for AUC in CYP2C19 normal metabolisers. The accumulation depends on the metabolism status for CYP2C19 with the largest accumulation observed in CYP2C19 poor metabolisers. At steady-state, the peak-to-trough plasma concentration ratio with once daily dosing is approximately 1.5.

Following a single 25 mg dose of ^{14}C labelled mavacamten in CYP2C19 normal metabolisers, 7% and 85% of the total radioactivity was recovered in the faeces and urine of CYP2C19 normal metabolisers, respectively. Unchanged active substance accounted for approximately 1% and 3% of the administered dose in the faeces and urine, respectively.

CYP2C19 phenotype
Polymorphic CYP2C19 is the main enzyme involved in the metabolism of mavacamten. An individual carrying two normal function alleles is a CYP2C19 normal metaboliser (e.g., *1/*1). An individual carrying two non-functional alleles is a CYP2C19 poor metaboliser (e.g., *2/*2, *2/*3, *3/*3). The incidence of CYP2C19 poor metaboliser phenotype ranges from approximately 2% in Caucasian to 18% in Asian populations.

Linearity/non-linearity

Exposure to mavacamten increased approximately dose proportionally between 2 mg and 48 mg and is expected to result in dose proportional exposure increase across the therapeutic range of 2.5 mg to 5 mg in CYP2C19 poor metabolisers and 2.5 mg to 15 mg in CYP2C19 intermediate to ultra-rapid metabolisers.

Special populations

No clinically significant differences in the PK of mavacamten were observed using population PK modelling based on age, sex, race or ethnicity.

Hepatic impairment
A single dose PK study was conducted in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, as well as a control group with normal hepatic function. Mavacamten exposures (AUC) increased 3.2-fold and 1.8-fold in patients with mild and moderate impairment, respectively, compared to patients with normal hepatic function. There was no effect of hepatic function on C_{max}, consistent with no change in the rate of absorption and/or volume of distribution. The amount of mavacamten excreted in urine in all 3 studied groups was 3%. A dedicated PK study has not been conducted in patients with severe (Child-Pugh class C) hepatic impairment.

Renal impairment
Approximately 3% of a mavacamten dose is excreted in the urine as parent substance. A population PK analysis, which comprised eGFR down to 29.5 mL/min/1.73m^2, demonstrated no correlation between renal function and exposure. A dedicated PK study has not been conducted in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Toxicology findings were generally related to adverse reductions on cardiac function consistent with exaggerated primary pharmacology in healthy animals. These effects occurred at clinically relevant exposures.

Reproductive toxicity and fertility

In reproductive toxicity studies, there was no evidence of effects of mavacamten on mating and fertility in male or female rats or in the viability and fertility of offspring of dams at any dose tested. However, plasma exposures (AUC) of mavacamten at the highest doses tested were less than in humans at the maximum recommended human dose (MRHD).

Embryo-foetal and postnatal development

Mavacamten adversely affected embryo-foetal development in rats and rabbits. When mavacamten was administered orally to pregnant rats during the period of organogenesis, decreased mean foetal

body weight, increases in post implantation loss, and foetal malformations (visceral and skeletal) were observed at clinically relevant exposures. Visceral malformations involved heart malformation in foetuses, including one total *situs inversus*, while skeletal malformations were manifested mostly as increased incidences of fused sternebrae.

When mavacamten was administered orally to pregnant rabbits during the period of organogenesis, visceral and skeletal malformations were noted, consisting of malformations of the great vessels (dilatation of pulmonary trunk and/or aortic arch), cleft palate and higher incidences of fused sternebrae. Maternal plasma exposure levels (AUC) at the no effect dose level for embryo-foetal development in both species were less than those in humans at the MRHD.

In a pre- and post-natal development study, administration of mavacamten to pregnant rats from gestation day 6 to lactation/post-partum day 20 did not result in adverse effects in the dams or offspring exposed daily from before birth (in utero) through lactation. The maternal exposure was less than the MRHD. No information is available on the excretion of mavacamten in animal milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Silica, colloidal hydrated
Mannitol (E421)
Hypromellose (E464)
Croscarmellose sodium (E468)
Magnesium stearate

Capsule shell

All strengths
Gelatin
Titanium dioxide (E171)

CAMZYOS 2.5 mg hard capsules
Iron oxide black (E172)
Iron oxide red (E172)

CAMZYOS 5 mg hard capsules
Iron oxide yellow (E172)

CAMZYOS 10 mg hard capsules
Iron oxide red (E172)

CAMZYOS 15 mg hard capsules
Iron oxide black (E172)

Printing ink

Iron oxide black (E172)
Shellac (E904)
Propylene glycol (E1520)
Ammonia solution, concentrated (E527)
Potassium hydroxide (E525)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blister containing 14 hard capsules.

Pack size of 14, 28 or 98 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1716/001-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 June 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of CAMZYOS in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.
The educational programme is aimed to educate Healthcare Professionals (HCPs) and patients on important risks associated with CAMZYOS.
The MAH shall ensure that in each Member State where CAMZYOS is marketed, all HCPs who prescribe CAMZYOS have access to/are provided with the Healthcare Professional Information Pack:
- Information on where to find the latest Summary of Product Characteristics (SmPC)
- HCP Checklist

- Patient Guide
- Patient Card

The HCP Checklist will contain the following messages:

Prior to starting treatment
For patients of childbearing potential
- Confirm a negative pregnancy test;
- Educate on the risk of embryo-foetal 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 6 months following discontinuation;
- Instruct patients to contact you or another member of your healthcare team immediately if they become pregnant or suspect they may be pregnant.

For all patients
- Complete an echocardiogram assessment and confirm the patient's left ventricular ejection fraction (LVEF) is ≥ 55% before starting treatment;
- Patients should be genotyped for CYP2C19 phenotype in order to determine appropriate CAMZYOS dose;
- Assess for potential interactions involving CAMZYOS and any medicine (including prescription and over-the-counter medicines), herbal supplements and grapefruit juice. Detailed guidance on dose modifications/contraindications with concomitant medicines, based on the patient's CYP2C19 phenotype status, is included in the Summary of Product Characteristics (Table 1 and Table 2 of Section 4);
- Inform the patient of the risk of heart failure associated with CAMZYOS and that they must consult their healthcare professional 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 risk of potential 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;
- Provide the patient with the Patient Guide and highlight the Patient Card within the guide.

During treatment at each clinical visit (as described in the Summary of Product Characteristics)
For patients of childbearing potential
- Remind patients of the risk of embryo-foetal toxicity associated with CAMZYOS;
- Counsel on the need to avoid pregnancy and the need for an effective form of contraception during treatment and for 6 months following discontinuation;
- Periodically check pregnancy status throughout treatment;
- Instruct patients to contact you or another member of your healthcare team immediately if they become pregnant or suspect they may be pregnant.

For all patients
- Confirm LVEF is ≥ 50% by echocardiogram assessment. If at any visit LVEF is < 50%, interrupt treatment for at least 4 weeks and until LVEF is ≥ 50%;
- Assess the LVOT gradient with Valsalva manoeuvre and adjust the dose per the guidance provided in the Summary of Product Characteristics Section 4.2;
- Assess the patient for signs, symptoms and clinical findings of heart failure per the guidance provided in the Summary of Product Characteristics Sections 4.2 and 4.4;
- Assess for intercurrent illnesses such as infections or arrhythmia (e.g., atrial fibrillation or other uncontrolled tachyarrhythmia);
- Assess for interactions involving CAMZYOS and any medicine (including prescription and over-the-counter medicines), herbal supplements and grapefruit juice that the patient has newly started, has changed the dose of or plans on taking in the future. Detailed guidance on dose modifications/contraindications with concomitant medicines, based on the patient's CYP2C19 phenotype status, is included in the Summary of Product Characteristics (Table 1 and Table 2 of Section 4);

- 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 the risks of potential interactions involving CAMZYOS;
- Counsel the patient on actions to take in case of an overdose and missed or delayed doses;
- Provide the patient with the Patient Guide and Patient Card if needed.

After treatment
For patients of childbearing potential
- Counsel patients on the need to avoid pregnancy and the need for an effective form of contraception for 6 months following discontinuation of CAMZYOS.

The Patient Card will contain the following key messages:

- Patient instructions: Carry this card with you at all times. Tell any healthcare professional who sees you that you are taking CAMZYOS.
- CAMZYOS is indicated for the treatment of symptomatic obstructive hypertrophic cardiomyopathy. Refer to the Patient Guide and package leaflet for more information, or contact <insert local BMS contact>.

Safety information for patients of childbearing potential (to appear first on the card):
- CAMZYOS may cause harm to an unborn baby if used during pregnancy.
- CAMZYOS must not be taken if you are pregnant or are of childbearing potential and are not using an effective method of contraception.
- If you are able to get pregnant, you must use an effective method of contraception throughout treatment and for 6 months after your last dose.
- Talk to your doctor if you are considering becoming pregnant.
- If you suspect you may be pregnant or are pregnant, you must inform your prescriber or doctor immediately.

Safety information for all patients:
- Tell your prescriber or doctor or seek other medical attention immediately if you experience new or worsening symptoms of heart failure, including shortness of breath, chest pain, fatigue, a racing heart (palpitations), or leg swelling.
- Tell your prescriber or doctor of any new or existing medical conditions.
- Tell your prescriber, doctor, or pharmacist about your treatment with CAMZYOS before starting any new medicines (including prescriptions and those available over-the-counter) or herbal supplements, since some of them can increase the amount of CAMZYOS in your body and make it more likely for you to get side effects (some of which may be severe). Do not stop taking or change the dose of any medicine or herbal supplement that you are already taking without talking to your doctor or pharmacist first, as other medicines can affect the way CAMZYOS works.

Please complete this section or ask your prescriber of CAMZYOS to complete it.
Patient's name:
Name of prescriber:
Office phone number:
After-hours phone number:
Hospital name (if applicable):

The Patient Guide will contain the following key messages:

Embryo-foetal toxicity risk messages listed first as a tear out page:
If you are of childbearing potential, please review the information below before you start treatment with CAMZYOS and keep this page for your reference.

- CAMZYOS must not be taken if you are pregnant or if you are of childbearing potential and are not using an effective method of contraception (birth control) as CAMZYOS may cause harm to an unborn baby.
- If you are able to get pregnant, you will need a confirmed negative pregnancy test before you start taking CAMZYOS.
- You must use an effective method of contraception throughout treatment and for 6 months after your last dose of CAMZYOS. You should discuss with your doctor which method(s) of contraception is/are the most suitable for you.
- Talk to your doctor if you are considering becoming pregnant.
- If you suspect you may be pregnant or are pregnant while receiving CAMZYOS, tell your prescriber or doctor immediately. You prescriber or doctor will discuss your treatment options with you.

On the following pages:

- Carry the Patient Card with you at all times and tell any healthcare professional who sees you that you are taking CAMZYOS;
- Brief description of echocardiograms and why they are important;
- CAMZYOS and heart failure
    - Heart failure due to systolic dysfunction is a serious and sometimes fatal condition.
    - Tell your prescriber or doctor, or seek other medical attention immediately if you experience new or worsening symptoms of heart failure, including shortness of breath, chest pain, fatigue, a racing heart (palpitations), or leg swelling.
    - Tell your prescriber or doctor of any new or existing medical condition(s) you experience before and during treatment with CAMZYOS.
- CAMZYOS and interactions
    - Some medicines, including those available over-the-counter, and some herbal supplements can affect the amount of CAMZYOS in your body and make it more likely for you to get side effects (some of which may be severe).
    - Tell your prescriber, doctor, or pharmacist about all of the prescription medicines, over-the-counter medicines and herbal supplements you take, even if you do not take them every day.
    - Do not start taking, stop taking, or change the dose of any of your medicines or herbal supplements without talking to your prescriber, doctor, or pharmacist.
    - Some examples of products that may affect how much CAMZYOS is in your body are shown in Table 1. Please note, these examples are a guide and are not considered a comprehensive list of all possible medicines that may fit this category. Intermittent use of products that might affect the levels of CAMZYOS in your body include prescription and over-the-counter medicines, herbal supplements and grapefruit juice is not recommended. Products listed in Table 1 “Examples of products that may affect CAMZYOS”:
        - Omeprazole, esomeprazole
        - Verapamil, diltiazem
        - Clarithromycin, rifampicin
        - Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
        - Fluoxetine, fluvoxamine
        - Ritonavir, cobicistat
        - Grapefruit juice
- When should I seek medical attention
    - Tell any healthcare professional who sees you if any side effects occur while taking CAMZYOS, even those not discussed in this Patient Guide.
    - Tell your prescriber or doctor, or seek other medical attention immediately if you experience new or worsening symptoms of heart failure, including shortness of breath, chest pain, fatigue, a racing heart (palpitations), or leg swelling.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

CAMZYOS 2.5 mg hard capsules
mavacamten

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 2.5 mg of mavacamten.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

14 hard capsules
28 hard capsules
98 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1716/001 (Pack size of 14 hard capsules)
EU/1/23/1716/002 (Pack size of 28 hard capsules)
EU/1/23/1716/009 (Pack size of 98 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CAMZYOS 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

CAMZYOS 2.5 mg capsules
mavacamten

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

CAMZYOS 5 mg hard capsules
mavacamten

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 5 mg of mavacamten.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

14 hard capsules
28 hard capsules
98 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1716/003 (Pack size of 14 hard capsules)
EU/1/23/1716/004 (Pack size of 28 hard capsules)
EU/1/23/1716/010 (Pack size of 98 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CAMZYOS 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

CAMZYOS 5 mg capsules
mavacamten

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

CAMZYOS 10 mg hard capsules
mavacamten

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10 mg of mavacamten.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

14 hard capsules
28 hard capsules
98 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1716/005 (Pack size of 14 hard capsules)
EU/1/23/1716/006 (Pack size of 28 hard capsules)
EU/1/23/1716/011 (Pack size of 98 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CAMZYOS 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

CAMZYOS 10 mg capsules
mavacamten

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

CAMZYOS 15 mg hard capsules
mavacamten

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 15 mg of mavacamten.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

14 hard capsules
28 hard capsules
98 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1716/007 (Pack size of 14 hard capsules)
EU/1/23/1716/008 (Pack size of 28 hard capsules)
EU/1/23/1716/012 (Pack size of 98 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CAMZYOS 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

CAMZYOS 15 mg capsules
mavacamten

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will give you a Patient Card and Patient Guide. Read it carefully and follow the instructions on it.
- Always show the Patient Card to the doctor, pharmacist or nurse when you see them or if you go to hospital.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CAMZYOS is and what it is used for

What CAMZYOS is
CAMZYOS contains the active substance mavacamten. Mavacamten is a reversible cardiac myosin inhibitor, meaning that it changes the action of the muscle protein myosin in heart muscle cells.

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

About obstructive hypertrophic cardiomyopathy
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 that you are about to faint, fainting (syncope) and swelling of the ankles, feet, legs, abdomen and/or veins in the neck.

How CAMZYOS works
CAMZYOS works by reducing excess contraction of the heart and the obstruction to blood flow to the body. As a result, it may improve your symptoms and your ability to be active.

2. What you need to know before you take CAMZYOS

Do not take CAMZYOS if:
- you are allergic to mavacamten or any of the other ingredients of this medicine (listed in section 6).
- you are pregnant or a woman of childbearing potential not using effective contraception.
- if you are taking medicines which may increase the level of CAMZYOS in your blood such as:
  - oral medicines to treat fungal infections such as itraconazole, ketoconazole, posaconazole, voriconazole,
  - certain medicines to treat bacterial infections such as the antibiotics clarithromycin,
  - certain medicines to treat HIV infection such as cobicistat, ritonavir,
  - certain medicines to treat cancer such as ceritinib, idelalisib, tucatinib.

Ask your doctor if the medicine you are taking prevents you from taking mavacamten. See section "Other medicines and CAMZYOS"

Warnings and precautions

Routine tests
Your doctor will assess how well your heart is working (your heart function) using an echocardiogram (an ultrasound test that takes images of your heart) before your first dose and regularly during treatment with CAMZYOS. It is very important to keep these echocardiogram appointments, because your doctor needs to check the effect of CAMZYOS on your heart. Your treatment dose may need to be adjusted to improve your response or to reduce side effects.
If you are a woman who could become pregnant your doctor may perform a pregnancy test before starting treatment with CAMZYOS.
Your doctor may do a test to check how this medicine is broken down (metabolised) in your body as this may be used to guide your CAMZYOS treatment (see section 3).

Tell your doctor or pharmacist straight away:
- **if you get any of these symptoms during your treatment with CAMZYOS:**
  - new or worsening shortness of breath,
  - chest pain,
  - tiredness,
  - palpitations (a forceful heartbeat that may be rapid or irregular), or
  - leg swelling.

  These could be signs and symptoms of systolic dysfunction, a condition where the heart cannot pump with enough force, which can be life-threatening and lead to heart failure.
- **if you develop** a serious infection or irregular heart beat (arrhythmia) as this could increase your risk of developing heart failure.

Your doctor may need to do additional tests of your heart function, interrupt the treatment or change your dose, depending on how you feel.

Women of childbearing potential
If used during pregnancy, CAMZYOS can harm the unborn baby. Before you start treatment with CAMZYOS your doctor will explain the risk to you and ask you to do a pregnancy test in order to ensure that you are not pregnant. Your doctor will give you a card which explains why you should not become pregnant while taking CAMZYOS. It also explains what you should do to avoid becoming pregnant while you are taking CAMZYOS. You must use effective contraception during treatment and for 6 months after stopping treatment (see section "Pregnancy and breast-feeding").
If you do become pregnant while taking CAMZYOS, tell your doctor straight away. Your doctor will stop treatment (see "If you stop taking CAMZYOS" in section 3).

Children and adolescents
Do not give this medicine to children (aged below 18 years) because the effectiveness and safety of CAMZYOS have not been studied in children and adolescents.

Other medicines and CAMZYOS
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because some other medicines can affect the way CAMZYOS works.
Some medicines can increase the amount of CAMZYOS in your body and make it more likely for you to get side effects that may be severe. Other medicines can reduce the amount of CAMZYOS in your body and may reduce its beneficial effects.
In particular, before taking CAMZYOS tell your doctor or pharmacist if you are taking, have recently taken, or have changed the dose of any of the following medicines:

- some medicines used to reduce the amount of acid your stomach produces (cimetidine, omeprazole, esomeprazole, pantoprazole)
- antibiotics for bacterial infections (such as clarithromycin, erythromycin)
- medicines used to treat fungal infections (such as itraconazole, fluconazole, ketoconazole, posaconazole and voriconazole)
- medicines used to treat depression (such as fluoxetine, fluvoxamine, citalopram)
- medicines for HIV infections (such as ritonavir, cobicistat, efavirenz)
- rifampicin (an antibiotic for bacterial infections like tuberculosis)
- apalutamide, enzalutamide, mitotane, ceritinib, idelalisib, ribociclib, tucatinib (medicines used to treat certain types of cancer)
- medicines for fits (seizures) or epilepsy (such as carbamazepine and phenytoin, phenobarbital, primidone)
- St. John's wort (a herbal medicine for depression)
- medicines that affect your heart (such as beta blockers and calcium channel blockers e.g. verapamil and diltiazem)
- medicines that make your heart more resistant to abnormal activity (such as sodium channel blockers e.g. disopyramide)
- ticlopidine (a medicine to prevent heart attack and stroke)
- letermovir (a medicine to treat cytomegalovirus infections)
- norethindrone (a medicine to treat various menstrual problems)
- prednisone (steroid).

If you take or have taken any of these medicines, or have changed the dose, your doctor needs to closely monitor you, may need to change your dose of CAMZYOS, or consider alternative treatments.

If you are not sure whether you are taking any of the medicines mentioned above, ask your doctor or pharmacist before taking CAMZYOS. Before stopping or changing the dose of a medicine or starting a new medicine, tell your doctor or pharmacist.

Do not take any of the above medicines occasionally or once in a while (not on a regular schedule) since that could change the amount of CAMZYOS in your body.

CAMZYOS with food and drink
You should use caution when drinking grapefruit juice while on treatment with CAMZYOS as it may change the amount of CAMZYOS in your body.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
Do not take CAMZYOS during pregnancy, for 6 months before getting pregnant, or if you are a woman who could become pregnant and you are not using effective contraception. CAMZYOS may cause harm to your unborn baby. If you are a woman who could become pregnant, your doctor will inform you about this risk and will check if you are pregnant before starting treatment and regularly

during treatment. Your doctor will give you a card which explains why you should not become pregnant while taking CAMZYOS. If you become pregnant, think you may be pregnant or planning to become pregnant while taking CAMZYOS, tell your doctor right away.

Breast-feeding
It is not known if CAMZYOS passes through breastmilk. You must not breast-feed while taking CAMZYOS.

Driving and using machines
Mavacamten may have a small effect on your ability to drive and use machines. If you feel dizzy while taking this medicine, do not drive a vehicle, cycle or use any tools or machines.

CAMZYOS contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

3. How to take CAMZYOS

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

How much to take
The recommended starting dose is 2.5 mg or 5 mg taken by mouth once daily. Your doctor may do a test to check how this medicine is broken down (metabolised) in your body. The result may guide your CAMZYOS treatment. If you have liver problems, your doctor may also prescribe a reduced starting dose.

Your doctor will monitor how well your heart is working while you are taking CAMZYOS using echocardiograms and may change your dose (increase, lower, or temporarily stop) based on the results.

Your doctor will tell you how much CAMZYOS to take.
Your doctor will prescribe you a single daily dose of either 2.5 mg, 5 mg, 10 mg or 15 mg. The maximum single dose is 15 mg once daily.

Always take CAMZYOS as prescribed by your doctor.

The first echocardiogram will be done before you start treatment, and then again during follow-up visits at week 4, 8 and 12 to assess your response to CAMZYOS. Routine echocardiograms will then be done every 3 months or 6 months. If your doctor changes your dose of CAMZYOS at any point, an echocardiogram will be done 4 weeks afterwards to make sure you are receiving a beneficial dose.

Taking this medicine
- Swallow the capsule whole with a glass of water at about the same time each day.
- You can take the medicine with food or between meals.

If you take more CAMZYOS than you should
If you take more capsules than you should, contact your doctor or go to a hospital straight away if you have taken 3 to 5 times the recommended dose. If possible, take the medicine pack and this leaflet with you.

If you forget to take CAMZYOS
If you forget to take CAMZYOS at the usual time, take your dose as soon as you remember on the same day and take your next dose at the usual time the next day. Do not take a double dose to make up for a forgotten capsule.

If you stop taking CAMZYOS
Do not stop taking CAMZYOS unless your doctor tells you to. If you wish to stop taking CAMZYOS, notify your doctor to discuss the best way to do so.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor or pharmacist immediately if you get any of these symptoms during treatment with CAMZYOS:
- new or worsening shortness of breath, chest pain, tiredness, palpitations (a forceful heartbeat that may be rapid or irregular), or leg swelling. These could be signs and symptoms of systolic dysfunction (a condition where the heart cannot pump with enough force), which can lead to heart failure and be life-threatening. *(Common side effect)*

Very common (may affect more than 1 in 10 people)
- dizziness
- difficulty breathing

Common (may affect up to 1 in 10 people)
- fainting

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CAMZYOS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What CAMZYOS contains
- The active substance(s) is mavacamten. Each hard capsule contains either 2.5 mg, 5 mg, 10 mg or 15 mg of mavacamten.
- The other ingredients are:
  - capsule content: silica, colloidal hydrated, mannitol (E421), hypromellose (E464), croscarmellose sodium (E468, see section 2 “CAMZYOS contains sodium”), magnesium stearate

- capsule shell:
  CAMZYOS 2.5 mg hard capsules
  gelatin, titanium dioxide (E171), iron oxide black (E172), iron oxide red (E172)
  CAMZYOS 5 mg hard capsules
  gelatin, titanium dioxide (E171), iron oxide yellow (E172)
  CAMZYOS 10 mg hard capsules
  gelatin, titanium dioxide (E171), iron oxide red (E172)
  CAMZYOS 15 mg hard capsules
  gelatin, titanium dioxide (E171), iron oxide black (E172)
- printing ink: iron oxide black (E172), shellac (E904), propylene glycol (E1520), ammonia solution, concentrated (E527), potassium hydroxide (E525).

What CAMZYOS looks like and contents of the pack

- The CAMZYOS 2.5 mg, approximately 18.0 mm in length, hard capsules (capsules) have a light purple opaque cap and white opaque body imprinted in black ink with “2.5 mg” on the cap and “Mava” on the body.
- The CAMZYOS 5 mg, approximately 18.0 mm in length, hard capsules (capsules) have a yellow opaque cap and white opaque body imprinted in black ink with “5 mg” on the cap and “Mava” on the body.
- The CAMZYOS 10 mg, approximately 18.0 mm in length, hard capsules (capsules) have a pink opaque cap and white opaque body imprinted in black ink with “10 mg” on the cap and “Mava” on the body.
- The CAMZYOS 15 mg, approximately 18.0 mm in length, hard capsules (capsules) have a grey opaque cap and white opaque body imprinted in black ink with “15 mg” on the cap and “Mava” on the body.

The hard capsules are packaged in aluminium foil blisters containing 14 hard capsules.

Each pack contains either 14, 28 or 98 hard capsules. Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.