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

MYQORZO 5 mg film-coated tablets
MYQORZO 10 mg film-coated tablets
MYQORZO 15 mg film-coated tablets
MYQORZO 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MYQORZO 5 mg film-coated tablets

Each film-coated tablet contains 5 mg aficamten.

MYQORZO 10 mg film-coated tablets

Each film-coated tablet contains 10 mg aficamten.

MYQORZO 15 mg film-coated tablets

Each film-coated tablet contains 15 mg aficamten.

MYQORZO 20 mg film-coated tablets

Each film-coated tablet contains 20 mg aficamten.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

MYQORZO 5 mg film-coated tablets

Purple, round tablet debossed with “5” on one side and “CK” on the other side. Tablet size of approximately 4.84 mm in diameter.

MYQORZO 10 mg film-coated tablets

Purple, triangle tablet debossed with “10” on one side and “CK” on the other side. Tablet size of approximately 6.73 mm x 6.99 mm.

MYQORZO 15 mg film-coated tablets

Purple, pentagon tablet debossed with “15” on one side and “CK” on the other side. Tablet size of approximately 7.33 mm x 7.37 mm.

MYQORZO 20 mg film-coated tablets

Purple, oval tablet debossed with “20” on one side and “CK” on the other side. Tablet size of approximately 5.46 mm x 10.29 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MYQORZO 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, left ventricular ejection fraction (LVEF) should be assessed by echocardiography (see section 4.4). Initiation or up-titration of MYQORZO in patients with LVEF < 55% is not recommended. Regular LVEF and Valsalva left ventricular outflow tract gradient (LVOT-G) assessment should be performed during titration to achieve an appropriate target Valsalva LVOT-G, while maintaining LVEF ≥ 50%.

Posology

The dose range is 5 mg to 20 mg (either 5 mg, 10 mg, 15 mg, or 20 mg). The recommended starting dose is 5 mg orally once daily. A starting dose of 10 mg should be considered for patients with LVOT-G ≥ 100 mmHg. The dose should be increased every 2 to 8 weeks by 5 mg until a maintenance dose or the maximum dose of 20 mg is achieved. The maintenance dose is individualised based on the patient's LVEF and LVOT-G. Recommendations for dosing based on LVEF and LVOT-G criteria are in Table 1.

Table 1: Dose adjustment of aficamten

LVEF	Valsalva LVOT-G	Dose adjustment
≥ 55%	≥ 30 mmHg	Increase dose by 5 mg (up to the maximum dose of 20 mg once daily)
≥ 55%	< 30 mmHg	Maintain dose
< 55% and ≥ 50%	Any	Maintain dose
< 50% and ≥ 40%	Any	Decrease dose by 5 mg[1] Interrupt treatment for 7 days for 5 mg dose
< 40%	Any	Interrupt treatment for at least 7 days.

[1] Dose decrease as follows: from 20 mg to 15 mg; from 15 mg to 10 mg; from 10 mg to 5 mg

An echocardiographic assessment should be performed 2 to 8 weeks after initiation of treatment, any dose adjustment, or treatment interruption. After a treatment interruption when LVEF < 40%, treatment should be resumed with a dose reduced by 5 mg when LVEF ≥ 55%. If at 5 mg and LVEF < 50%, treatment should be interrupted for 7 days, and treatment can be resumed at 5 mg when LVEF ≥ 55% (see Table 1).

After the maintenance dose has been established, LVEF and Valsalva LVOT-G should be assessed every 6 months, or every 3 months in patients with LVEF ≥ 50% to < 55%. Consider monitoring LVEF and adjust dose per Table 1, as needed, in patients with intercurrent illness (e.g. severe infection

or COVID-19), new arrhythmia (e.g. new or uncontrolled atrial fibrillation or other uncontrolled tachyarrhythmia) or any other conditions that may impair systolic function. Dose increases are not recommended until intercurrent illness or new arrythmia has resolved or stabilised.

Discontinuation of aficamten may result in recurrence of HCM symptoms. Gradual dose reduction may attenuate the rate of symptom recurrence following treatment discontinuation (see section 4.4).

Dose modification with concomitant medicinal products

Concomitant use with moderate CYP2C9 inhibitors that are also moderate-to-strong inhibitors of CYP2D6 or CYP3A e.g. more than a single dose of fluconazole or strong inducers e.g. rifampicin is contraindicated (see section 4.3).

Concomitant use of aficamten with strong CYP2C9 inhibitors should be avoided. If coadministration cannot be avoided, the dose of aficamten should be reduced to 5 mg and LVEF and LVOT-G assessed every 4 to 8 weeks until a new maintenance dose of aficamten in presence of the inhibitor has been reached (see section 4.5).

The recommended starting dose is 5 mg once daily in patients who are on stable therapy with a weak CYP2C9 inhibitor that is also a moderate-to-strong CYP2D6 or CYP3A inhibitor (e.g. voriconazole, fluvoxamine). The maintenance dose of aficamten should not exceed 15 mg.

For patients who initiate a weak CYP2C9 inhibitor that is also a moderate-to-strong CYP2D6 or CYP3A inhibitor, the dose of MYQORZO should be reduced to 5 mg if they are currently receiving 15 mg or 20 mg. Concomitant use should be avoided if patients are currently receiving MYQORZO 5 mg or 10 mg. The maintenance dose of aficamten should not exceed 15 mg. LVEF and LVOT-G should be assessed every 4 to 8 weeks until a new maintenance dose of aficamten in presence of the inhibitor has been reached (see section 4.5).

For patients who intend to discontinue a moderate-to-strong CYP2C9 or CYP3A inducer (e.g. carbamazepine), the dose should be reduced (from 20 mg to 10 mg; from 15 mg to 5 mg; from 10 mg to 5 mg) according to Table 2 (see also section 4.5). For patients currently receiving 5 mg, maintain the 5 mg dose. LVEF and LVOT-G should be assessed after inducer discontinuation. Assessment of LVEF and LVOT-G and dose titration according to Table 1 is recommended.

Table 2: Dose modification of aficamten with concomitant medicinal products

Concomitant medicinal product	**Initiating aficamten while on stable medicinal product treatment**	**Initiating medicinal product while on stable aficamten treatment**	**Discontinuing medicinal product while on stable aficamten treatment**
Inhibitors			
Any strong CYP2C9 inhibitor (e.g. sulfaphenazole)	Avoid concomitant administration. If coadministration cannot be avoided, reduce the dose of aficamten to 5 mg and assess LVEF and LVOT-G every 4 to 8 weeks until a new maintenance dose of aficamten in presence of the inhibitor has been reached (see section 4.5).		
Any moderate CYP2C9, and moderate-to-strong CYP2D6 or CYP3A, inhibitor (e.g. fluconazole, adagrasib)	Coadministration is contraindicated for more than a single dose of fluconazole (see section 4.3). Adagrasib coadministration is contraindicated (see section 4.3).		
Any weak CYP2C9 and moderate-to-strong CYP2D6 or CYP3A inhibitor (e.g.	Initiate aficamten at the recommended starting dose of 5 mg once daily.	Reduce the dose of aficamten from 20 mg	No dose adjustment needed.

fluvoxamine, voriconazole)		to 5 mg, from 15 mg to 5 mg. Avoid if on 10 mg or 5 mg aficamten (see section 4.5).	
	The maintenance dose of aficamten should not exceed 15 mg. LVEF and LVOT-G should be assessed every 4 to 8 weeks until a new maintenance dose of aficamten in presence of the inhibitor has been reached (see section 4.5).		
	Assess LVEF and LVOT-G, and dose titrate/monitor according to Table 1.		
Inducers			
Moderate CYP2C9 and strong CYP3A inducer (e.g. rifampicin)	Concomitant use with rifampicin is contraindicated (see section 4.3).		
Any moderate-to-strong CYP2C9 or CYP3A inducer (e.g. carbamazepine)	Initiate aficamten at the recommended starting dose of 5 mg once daily.	No dose adjustment needed.	Reduce dose of aficamten from 20 mg to 10 mg, from 15 mg to 5 mg, from 10 mg to 5 mg. No dose adjustment is required for patients currently receiving 5 mg of aficamten (see section 4.5).
	Assess LVEF and LVOT-G, and dose titrate/monitor according to Table 1.		

Missed doses

If a dose is missed, it should be taken as soon as possible on the same day. The next scheduled dose should be taken at the usual time the following day. Two doses should not be taken the same day.

Elderly

No dose adjustment is required for patients aged 65 years and older (see section 5.2).

Renal impairment

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

Hepatic impairment

No dose adjustment to the standard recommended dose and titration schedule is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. No dose recommendation can be made for patients with severe hepatic impairment (Child-Pugh class C) because aficamten has not been studied in patients with severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of aficamten in children and adolescents below 18 years have not been established. No data are available.

Method of administration

For oral use.

Treatment should be taken once daily with or without meals. The tablet should be swallowed whole with water and not split, crushed, or chewed as these methods have not been studied.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Moderate CYP2C9 inhibitors that are also moderate-to-strong inhibitors of CYP2D6 or CYP3A: e.g. adagrasib and more than a single dose of fluconazole (see section 4.5).
- Strong CYP3A4 inducers that are also moderate CYP2C9 inducers: rifampicin and St. John's wort (see section 4.5).

4.4 Special warnings and precautions for use

Systolic dysfunction defined as LVEF < 50%

Aficamten reduces cardiac contractility and LVEF. Heart failure due to systolic dysfunction can occur in patients receiving cardiac myosin inhibitors (see section 4.8).

Patients who experience a severe intercurrent illness (e.g. serious infection) or arrhythmia (e.g. new or uncontrolled atrial fibrillation) may be at greater risk of developing systolic dysfunction and heart failure. Additional monitoring should be considered for asymptomatic LVEF reduction with intercurrent illnesses, and arrhythmias (see section 4.2).

The patient's clinical status and LVEF should be assessed prior to and regularly during treatment and the dose should be adjusted accordingly. New or worsening arrhythmia, dyspnoea, chest pain, fatigue, leg oedema, or elevations in N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be signs and symptoms of heart failure and should also prompt an evaluation of cardiac function.

Heart failure or loss of response to aficamten due to interactions

Aficamten is metabolised by CYP2C9, CYP2D6 and CYP3A enzymes. Initiation of certain medicinal products that inhibit multiple P450 pathways of aficamten elimination (e.g. fluconazole, voriconazole, fluvoxamine), and strong CYP2C9 inhibitors may lead to increased blood concentrations of aficamten, and increase the risk of heart failure due to systolic dysfunction (see sections 4.2, 4.3 and 4.5).

Discontinuation of moderate-to-strong CYP3A inducers and moderate-to-strong CYP2C9 inducers may lead to increased blood concentrations of aficamten, and increase the risk of heart failure due to systolic dysfunction. Conversely, initiation of certain medicinal products that induce P450s (e.g. rifampicin, moderate-to-strong CYP3A or CYP2C9 inducers) may lead to decreased blood concentrations of aficamten and potential loss of effectiveness (see sections 4.2, 4.3 and 4.5).

Patients should be advised of the potential for drug interactions and to inform their healthcare professional of all concomitant medicinal products prior to and during MYQORZO treatment.

Pregnancy

There is no evidence for the use of aficamten in pregnant women, and animal studies are insufficient to inform maternal or embryo-foetal risk in humans. Foetal harm cannot be ruled out (see sections 4.6 and 5.3).

Recurrence of HCM symptoms with discontinuation

Discontinuation of aficamten may result in recurrence of HCM symptoms. In SEQUOIA-HCM, cardiovascular adverse events were reported more commonly in the aficamten group compared to the placebo group with an onset during the washout period [n=23 (16.2%) versus n=9 (6.5%)], 3 had serious events of worsening HCM when stopping aficamten. Careful monitoring during discontinuation is recommended. Gradual dose reduction may attenuate the rate of symptom recurrence following treatment discontinuation (see section 4.2).

Excipient with known effect

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

If a treatment with negative inotrope effect, such as non-dihydropyridine calcium channel blockers or disopyramide, is initiated, or if the dose of a medicinal product with negative inotrope effect is increased in a patient receiving aficamten, close medical supervision and monitoring of LVEF should be provided until stable doses and clinical response have been achieved (see section 4.2).

Pharmacokinetic interactions

Effect of other medicinal products on aficamten

Aficamten is primarily metabolised by CYP2C9 and, to a lesser extent by CYP2D6 and CYP3A, with minimal CYP2C19 involvement. Concomitant administration of certain medicinal products that inhibit multiple P450 pathways of aficamten elimination, strong inhibitors of CYP2C9, and moderate-to-strong inducers of CYP2C9 or CYP3A, may affect the exposure of aficamten (see Table 3).

Concomitant use contraindicated

Coadministration of aficamten with more than a single dose of fluconazole and adagrasib is contraindicated (see section 4.3). Fluconazole (400 mg once daily), which is a moderate CYP2C9, strong CYP2C19, and moderate CYP3A inhibitor) increased aficamten AUC by 278%. Adagrasib a moderate CYP2C9, strong inhibitor of CYP3A4 and moderate inhibitor of CYP2D6 is expected to result in comparable or higher increased aficamten exposures as fluconazole.

Coadministration of aficamten with medicinal products that are strong inducers of CYP3A and are also moderate CYP2C9 inducers such as rifampicin or St. John's wort (*Hypericum perforatum*) may result in decreased plasma concentrations of aficamten leading to loss of therapeutic effect (see section 4.3).

Concomitant use not recommended

Avoidance is recommended for strong CYP2C9 inhibitors (e.g. sulfaphenazole) (see section 4.2).

Other interactions

Interactions of aficamten and potential co-administered medicinal products are listed in Table 3 below (increase is indicated as "↑", decrease as "↓"). These interactions are based on either drug interaction studies or physiologically based pharmacokinetic predicted interactions due to the expected magnitude of interaction.

Table 3: Interactions between aficamten and other medicinal products

Medicinal product by mechanism	Effects on aficamten levels Mean percent change in AUC	Recommendation concerning coadministration with aficamten
Strong CYP3A4 inhibitor **itraconazole 200 mg once daily**	26% ↑	This increase is not considered to be clinically relevant and does not necessitate dose adjustment of aficamten.
Strong CYP2D6 inhibitor **paroxetine 40 mg once daily**	27% ↑	This increase is not considered to be clinically relevant and does not necessitate dose adjustment of aficamten.
Strong CYP2D6 and strong CYP2C19 inhibitor **fluoxetine 40 mg once daily**	31% ↑	This increase is not considered to be clinically relevant and does not necessitate dose adjustment of aficamten.
Strong CYP2C9 inhibitor **sulfaphenazole**	Interaction not studied Coadministration of a strong CYP2C9 inhibitor is expected to increase aficamten exposure.	Coadministration should be avoided. If coadministration cannot be avoided, reduce the dose of aficamten to 5 mg and assess LVEF and LVOT-G every 4 to 8 weeks until a new maintenance dose of aficamten in presence of the inhibitor has been reached. (section 4.2, Table 1) The half-life of aficamten is expected to be increased (~7 to 10 days) in combination with strong CYP2C9 inhibitor. A new aficamten steady-state would then be achieved 5 to 7 weeks after initiation of inhibitor.
Moderate CYP2C9 inhibitors that are also moderate-to-strong inhibitors of CYP2D6 or CYP3A **fluconazole 400 mg once daily** **e.g. adagrasib**	278% ↑ Interaction with adagrasib is not studied but similar increase in aficamten exposure expected as caused by fluconazole.	Coadministration is contraindicated for adagrasib and more than a single dose of fluconazole (section 4.3) For coadministration of fluconazole 150 mg single dose, no dose adjustment of aficamten is necessary. For once weekly use, assess LVEF and LVOT-G every 4 to 8 weeks until a new maintenance dose of aficamten in the presence of fluconazole has been reached.
Weak CYP2C9 inhibitors that are also moderate-to-strong inhibitors of CYP2D6 or CYP3A **fluvoxamine**	Interactions not studied.	Caution, adjust the dose of aficamten (section 4.2). Assess LVEF and LVOT-G every 4 to 8 weeks until a new maintenance dose of aficamten

voriconazole	Coadministration of fluvoxamine and voriconazole is expected to increase aficamten exposure.	in presence of the inhibitor has been reached (section 4.2, Table 1). The half-life of aficamten is expected to be increased (~1 week). A new aficamten steady-state would then be achieved by 4 to 6 weeks after initiation of inhibitor.
Weak CYP2C9 inhibitors that are also weak to moderate inhibitors of CYP2D6 or CYP3A **amiodarone**	Amiodarone has been co-administered in the clinical studies. Aficamten exposure may increase.	Amiodarone has been co-administered in the clinical studies. Most patients had a maintenance aficamten dose of 5 and 10 mg. Assessment of LVEF and LVOT-G every 4 to 8 weeks is recommended when starting or stopping with amiodarone concomitant use. Amiodarone has a long half-life therefore interactions can linger for months after ending of amiodarone treatment.
Strong CYP3A4 inducers that are also -moderate CYP2C9 inducers **rifampicin** **St. John's wort**	Interactions not studied. Coadministration of rifampicin and other strong CYP3A that are also moderate CYP2C9 inducers is expected to decrease aficamten exposure leading to loss of therapeutic effect	Contraindicated (section 4.3)
Moderate-to-strong CYP3A4 and CYP2C9 inducers **carbamazepine 300 mg twice daily** **e.g. rifabutin, efavirenz**	51% ↓ Interactions not studied but similar effects expected.	This decrease in aficamten exposure may lead to less therapeutic effect. Maintenance aficamten dose may be increased up to a maximal dose of 20 mg once daily.

Effect of aficamten on other medicinal products

Coadministration of aficamten is not expected to cause clinically significant drug-drug interactions with sensitive substrates of CYP enzymes or drug transporters.

Aficamten increased total dabigatran exposure by 26% and therefore, aficamten is not a clinically significant P-glycoprotein inhibitor.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment.

Pregnancy

There is no evidence from the use of aficamten in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). A careful benefit/risk evaluation is required before use and during pregnancy and MYQORZO should not be used during pregnancy unless the clinical condition of the woman requires treatment with aficamten.

Based on the mode of action of aficamten, a negative inotropic effect on the foetal heart cannot be ruled out. If a woman is treated with aficamten during pregnancy, regular foetal echocardiography (e.g. every 2 weeks) is recommended. Dose reduction or discontinuation of aficamten should be considered if any sign of foetal cardiac dysfunction is observed, also considering the maternal half-life of aficamten (approximately 3.3 days, see section 5.2). Monitoring of the woman should consider the circulatory adaptations to pregnancy.

Breast-feeding

It is unknown whether aficamten/metabolites are excreted in human milk. There is insufficient information on the excretion of aficamten/metabolites in animal milk and a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from MYQORZO therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human fertility data on aficamten are available. No effects on fertility were observed in animal studies.

4.7 Effects on ability to drive and use machines

Aficamten has minor influence on the ability to drive and use machines. Dizziness may occur during use of aficamten. 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 observed with aficamten are dizziness (4.2%), systolic dysfunction defined as LVEF < 50% (3.5%), palpitations (7%) and hypertension (7.7%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on all-cause adverse events frequencies of 142 patients exposed to aficamten in SEQUOIA-HCM study (see section 5.1) with a median treatment duration of 24.1 weeks (range 3.9 to 29.4 weeks).

The adverse reactions included in Table 4 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 4: Adverse reactions

System organ class	Adverse reaction	Frequency
Nervous system disorders	Dizziness	Common
Cardiac disorders	Systolic dysfunction[1]	Common
	Palpitations	Common
Vascular disorders	Hypertension	Common

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

Description of selected adverse reactions

Systolic dysfunction

In SEQUOIA-HCM study, during the 24-week treatment period, 3.5% patients in the aficamten group experienced a reversible dose related reduction in LVEF to < 50% (median 47%; range 34% to 49%). One patient in the aficamten group experienced an asymptomatic LVEF < 40%. Reductions in LVEF to < 50% did not require treatment interruption and were not associated with clinical heart failure (see section 4.4).

Effects on blood pressure

In SEQUOIA-HCM, adverse events of hypertension were reported more commonly in the aficamten group compared with the placebo group (7.7% versus 2.1%). The mean increases of blood pressure associated with aficamten treatment were 2.3 mmHg for systolic blood pressure, and 3.1 mmHg for diastolic blood pressure. Most reports of hypertension were in patients with a history of hypertension, and all reports were non-serious and mild or moderate in severity. Aficamten-associated increases in blood pressure are thought to be a consequence of relief of LVOT obstruction with improved cardiac output.

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

The highest single dose of aficamten 75 mg was administered to 1 healthy participant and resulted in LVEF of 35% at 1.5 hours post-dose that was asymptomatic, with recovery to LVEF of 52% at 4 hours post-dose. Treatment of overdose with consists of discontinuation of aficamten as well as medically supportive measures to maintain hemodynamic stability, including close monitoring of vital signs and LVEF and management of the clinical status of the patient. Overdose in humans can be life-threatening and result in asystole refractory to any medical intervention.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, Other cardiac preparations, ATC code: Not yet assigned

Mechanism of action

Aficamten is a reversible allosteric cardiac myosin inhibitor that binds directly to the motor domain of cardiac myosin and prevents it from entering the force-producing state. Nonclinical data indicate that aficamten is selective for the cardiac isoform of myosin compared to fast skeletal myosin. Specifically, aficamten inhibited bovine cardiac myofibrillar ATPase with approximately 5-fold higher potency than rabbit fast skeletal myofibrillar ATPase. It is designed to reduce the hypercontractility in the cardiac sarcomere fundamental to the pathophysiology of HCM. The consequent reduction in cardiac contractility reduces LVOT obstruction in HCM patients.

Pharmacodynamic effects

LVEF

In SEQUOIA-HCM study, the mean [standard deviation (SD)] resting LVEF at baseline was 74.8% (5.5%) for patients in the aficamten group and 74.8% (6.3%) in the placebo group. Consistent with the mechanism of action of aficamten, least squares (LS) mean [standard error (SE)] change from baseline in LVEF was -6.8% (0.6%) in the aficamten group and -2% (0.6%) in the placebo group at the end of the 24-week treatment period. Mean LVEF was similar between the aficamten and placebo groups 4 weeks after the end of treatment.

LVOT obstruction

In SEQUOIA-HCM study, the mean (SD) resting and Valsalva LVOT-G at baseline were 54.8 (27) and 82.9 (32) mmHg for patients in the aficamten group and 55.3 (32.2) and 83.3 (32.7) mmHg in the placebo group. At week 24, the LS mean (SE) changes from baseline in resting and Valsalva LVOT-G were -35.8 (2.1) mmHg and -48.1 (2.4) mmHg, respectively, for the aficamten group and 4.1(2.1) mmHg and 2.2 (2.4) mmHg respectively for the placebo group. Valsalva LVOT-G were similar to baseline for both treatment arms 4 weeks after the discontinuation from treatment.

Cardiac biomarkers

In SEQUOIA-HCM, geometric mean NT-proBNP and troponin I at baseline were 734.7 pg/mL and 17.1 ng/L for patients in the aficamten group and 709.8 pg/mL and 16.6 ng/L in the placebo group. At week 24, the proportional change from based in NT-proBNP and troponin I were 0.19 and 0.58, respectively, for the aficamten group and 0.99 and 1.01, respectively, for the placebo group. NT-proBNP and troponin I were similar to baseline for both treatment arms 4 weeks after the discontinuation from treatment.

Cardiac electrophysiology

The results of a thorough QT study demonstrated a lack of QTc prolongation across the therapeutic concentration range of aficamten. At a single dose of 50 mg (similar exposure as 20 mg daily dosing to steady-state), the upper limits of the predicted placebo-corrected change from baseline in QT interval corrected by Fridericia (ΔΔQTcF) 90% confidence interval for aficamten were all < 10 msec.

Clinical efficacy and safety

The efficacy of aficamten was evaluated in SEQUOIA-HCM study, a phase 3, multicentre, randomised, double-blind, placebo-controlled study in 282 adults (142 aficamten, 140 placebo) with symptomatic NYHA class II and III oHCM, LVEF ≥ 60%, and resting and peak Valsalva LVOT-G ≥ 30 and ≥ 50 mmHg at screening, respectively.

Patients with a known infiltrative or storage disorder causing cardiac hypertrophy such as Noonan syndrome, Fabry disease or amyloidosis were excluded.

Patients were randomised in a 1:1 ratio to receive either a starting dose of 5 mg of aficamten or placebo once daily for 24 weeks. Stratification factors included baseline use of beta blockers and cardiopulmonary exercise testing (CPET) ergometer (treadmill or cycle). At baseline, beta-blockers were used by 61.3% of patients, and non-dihydropyridine calcium channel blockers were used by 28.7% of participants. In addition, 12.8% of patients were taking disopyramide. Overall, 14.5% of patients were not taking any background medicinal product at baseline.

Overall, baseline demographics and disease characteristics were balanced between treatment groups. The study enrolled patients with a mean age of 59.1 years; (range 18 to 84 years), 59% male, 79% White, 19% Asian and 1% Black or African American. The mean, body mass index was 28.1 kg/m^2, mean resting heart rate of 66 bpm and mean blood pressure of 125/74 mmHg. In SEQUOIA-HCM there were 57 patients aged 65 years and older. No patients had undergone prior septal reduction therapy (SRT). At baseline, 76% of the randomised patients were NYHA class II and 24% were NYHA class III. The median LVEF was 75.6%, the mean resting LVOT-G was 55.1 mmHg, the mean Valsalva LVOT-G was 83.1 mmHg, and the mean Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) was 74.7.

Patients were initiated on aficamten at a dose of 5 mg once daily. Doses were individually titrated at weeks 2, 4 and 6 if Valsalva LVOT-G $\geq$ 30 mmHg and LVEF $\geq$ 55% in 5 mg intervals up to a maximum dose of 20 mg one daily. At week 24 in the aficamten group, 46% of patients were receiving a 20 mg dose, 35% were receiving a 15 mg dose, 15.3% were receiving a 10 mg dose and 3.6% were receiving a 5 mg dose.

Primary endpoint - peak oxygen uptake (pVO_2)

In SEQUOIA-HCM study, the primary endpoint of change from baseline in pVO_2 to week 24 was statistically significant and greater in the aficamten group compared with placebo, as shown in Table 5.

Secondary endpoints

The treatment effects of aficamten on health status, functional capacity, and LVOT obstruction were assessed by change in KCCQ-CSS, proportion of patients with $\geq$ 1 class improvement in NYHA functional class, change from baseline in Valsalva LVOT-G, proportion of patients with Valsalva LVOT-G $\leq$ 30 mmHg and duration of eligibility for septal reduction therapy (SRT). At week 24, patients receiving aficamten had greater improvement compared to the placebo group across all secondary points (Table 5).

Table 5: Analysis of endpoints from SEQUOIA-HCM study

Endpoints	Aficamten N=142	Placebo N=140
Change from baseline in pVO_2 by CPET		
Baseline (mL/min/kg), mean (SD)	18.4 (4.4)	18.6 (4.5)
Week 24		
LS mean (SE)	1.76 (0.25)	0.02 (0.25)
LS mean difference vs. placebo (95% CI)	1.74 (1.04, 2.44)	
p-value	< 0.0001	
Change from baseline in KCCQ-CSS[1]		
Baseline, mean (SD)	75.6 (18.4)	73.7 (17.6)
Week 12, n (%)	11.1 (0.9)	4 (0.9)
Difference (95% CI)	7 (4.5, 9.5)	
p-value	< 0.0001	
Week 24, n (%)	11.6 (1)	4.3 (1)
Difference (95% CI)	7.3 (4.6, 10.1)	
p-value	< 0.0001	
Proportion of patients with improvement of ≥ 10 points in KCCQ-CSS[1]		
Week 12, n (%)	63 (44.4)	33 (23.6)
Difference (95% CI)	20.8 (10, 31.6)	
p-value	< 0.001	
Week 24, n (%)	69 (48.6)	38 (27.1)
Difference (95% CI)	21.5 (10.6, 32.5)	
p-value	< 0.001	
Proportion of patients who remained eligible for SRT[4]		
Baseline	N = 32	N = 29
Week 24, n (%)	4 (12.5)	14 (48.3)
Difference (95% CI)	OR: 0.16 (0.03, 0.61) Difference: -36.5 (-58.5, -14.5)	
p-value	OR, p = 0.005 Difference, p = 0.002	
Duration of SRT eligibility[1]		
Days spent SRT-eligible during 24 weeks of treatment, n (%)	35.3 (7.9)	113.4 (8.1)
Difference (95% CI)	−78.1 (−99.8, −56.3)	
p-value	< 0.0001	
Change from baseline in Valsalva LVOT-G (mmHg)[1]		
Baseline, mean (SD)	83 (32)	83 (32.7)
Week 12, n (%)	-46 (2.4)	2.6 (2.4)
Difference (95% CI)	-48 (-55, -42)	
p-value	< 0.0001	
Week 24, n (%)	-48 (2.4)	2.2 (2.4)
Difference (95% CI)	-50 (-57, -44)	
p-value	< 0.0001	
Proportion of patients with Valsalva LVOT-G < 30 (mmHg)[4]		

Week 12, n (%)	74 (52.1)	8 (5.7)
Difference (95% CI)	OR: 18 (7.8, 44.4) Difference: 46.4 (37.3, 55.5)	
p-value	< 0.0001	
Week 24, n (%)	70 (49.3)	5 (3.6)
Difference (95% CI)	OR: 25.5 (10.1, 88.2) Difference: 45.7 (36.9, 54.5)	
p-value	< 0.0001	
Proportion of patients with ≥ 1 NYHA class improvement[4]		
Week 12, n (%)	69 (48.6)	25 (17.9)
Difference (95% CI)	OR: 4.6 (2.6, 8.4) Difference: 30.8 (20.6, 41)	
p-value	< 0.0001	
Week 24, n (%)	83 (58.5)	34 (24.3)
Difference (95% CI)	OR: 4.4 (2.6, 7.6) Difference: 34.2 (23.4, 45)	
p-value	< 0.0001	

CPET: Cardiac Pulmonary Exercise Test; KCCQ CSS: Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; NYHA: New York Heart Association; LVOT-G: left ventricular outflow tract gradient; SRT: septal reduction therapy

[1] LS means (SE) and LS mean difference (95% CI) presented for continuous endpoints.

[2] The KCCQ CSS measures patient-perceived physical limitations and symptoms associated with heart failure. The KCCQ CSS ranges from 0 to 100, with higher scores representing better health status.

[3] NYHA includes Classes I to IV.

[4] The number (percentage) of responders and rate difference (Diff) and common OR (exact 95% CI of the OR) are presented for binary endpoints.

A range of demographic characteristics, baseline disease characteristics, and baseline concomitant medicinal products (e.g. use of beta blockers) were examined for their influence on outcomes. Results of the primary analysis favoured aficamten consistently across all subgroups.

The effect of aficamten on the left ventricular outflow tract gradient after the Valsalva maneuver was relatively rapid, with a LS mean difference between the groups of −20 mm Hg (95% CI, −27.3 to −13.3) after 2 weeks.

Paediatric population

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

5.2 Pharmacokinetic properties

Aficamten exposure increases dose proportionally following multiple once-daily doses of 1 mg to 75 mg of aficamten. Aficamten pharmacokinetics was comparable between healthy participants and patients with oHCM: healthy participants demonstrated only 23% lower exposure than patients with oHCM. Geometric mean accumulation ratios for aficamten were similar across dose levels and ranged from 4.57 to 4.82.

Absorption

Aficamten is rapidly absorbed with a median time to maximum concentration (t_{max}) of 1.5 to 2 hours. Aficamten maximum concentration (C_{max}) and trough concentration (C_{trough}) after 20 mg once daily administration at steady-state were 336 and 288 ng/mL, respectively. The bioavailability of aficamten

after oral administration is unknown. No clinically significant differences in aficamten AUC and C_{max} were observed following its administration with a high-fat, high-calorie meal.

Distribution

Aficamten is approximately 90% bound to plasma proteins and demonstrates apparent volume of distribution of 309 L. The blood to plasma ratio of aficamten was 0.94.

Biotransformation

Aficamten is extensively metabolised in humans, primarily through CYP2C9 (50%) with contributions by CYP3A (26%) and CYP2D6 (21%), and minimal involvement of CYP2C19 (3%). Aficamten is primarily metabolised to 2 pharmacologically inactive metabolites, CK-3834282 and CK-3834283, that circulate at approximately 56% and 103% of parent in plasma, respectively.

CYP2C9 is a polymorphic enzyme. Literature data indicate that CYP2C9*2*3 and especially CYP2C9*3*3 variants result in less activity. Those variants still have 15-45% of the activity of normal metabolisers as demonstrated on the pharmacokinetics of several sensitive substrates. Since aficamten is also metabolised by CYP enzymes other than CYP2C9, and some CYP2C9 activity is remaining in patients with CYP2C9 poor metaboliser phenotype, no genotyping, nor genotype-dependent starting dose, is considered necessary.

Elimination

Aficamten has a median terminal half-life ($t_{½}$) and time to steady-state of approximately 80 hours and 17 days, respectively, in patients with oHCM. Most (~95%) patients with oHCM are expected to have a $t_{½}$ of less than 155 hours and to achieve steady-state by 33 days of daily aficamten dosing. At steady-state, the peak-to-trough plasma concentration ratio with once daily dosing is approximately 1.2. The total clearance is 2.6 L/h and the renal clearance is < 0.1% of total clearance.

Following a single 20 mg radiolabeled dose of aficamten, 32% (0.055% unchanged aficamten) was excreted in urine and 58% (5% unchanged aficamten) was excreted in faeces.

Special populations

Population pharmacokinetic analyses demonstrated no clinically meaningful differences in the pharmacokinetics of aficamten were observed based on age (18 to 83 years) or ethnicity.

Small but significant differences in aficamten exposure with sex and body weight were observed. Female patients demonstrated a 31% higher exposure than male patients. The highest body weight quartile of patients (105 kg) demonstrated a 44% lower aficamten exposure than the lowest body weight quartile of patients (64 kg).

Renal impairment

Population pharmacokinetic analyses demonstrated no clinically meaningful differences in the pharmacokinetics of aficamten (14 to 28% increase in exposure) based on mild to moderate (eGFR ≥ 30 mL/min) renal impairment. The effects of severe (eGFR < 30 mL/min) renal impairment are unknown.

Hepatic impairment

Based on phase 1 study, no clinically meaningful differences in the pharmacokinetics of aficamten in mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment are expected. Moderate hepatic impairment demonstrated no change in aficamten exposure. The effects of severe (Child-Pugh class C) hepatic impairment are unknown.

Paediatric population

The pharmacokinetics of aficamten have not been investigated in patients below 18 years of age.

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, carcinogenic potential.

Embryo-foetal and postnatal development

When aficamten was administered orally in an embryo-foetal toxicity study in the rat, increases in the number of early and late resorptions, decreases in group mean foetal body weight, and foetal abnormalities such as short tail (1 foetus) and kinked tail (2 foetuses) were observed at maternally toxic exposures 2.5x above the maximum recommended human dose (MRHD) of 20 mg of aficamten based on AUC. There were no aficamten-associated adverse effects on foetal growth, or foetal external or visceral variations observed at exposures 1.9x above the MRHD based on AUC..

When aficamten was administered orally in an embryo-foetal toxicity study in the rabbit, increases in the number of late resorptions were observed at maternally toxic exposures below the MRHD. As such this study is considered insufficient.

In a pre- and postnatal development study, aficamten was administered to maternal rats at doses up to 6 mg/kg/day during organogenesis through delivery and weaning, which is anticipated to be at an exposure close to the MRHD. At 6 mg/kg/day there were reductions in maternal body weight, increased heart weight, a reduction in the viability index in the pups, decreased mean group body weight, suspected dehydration, no milk band present and bent tail. At the NOAEL of 1.5 mg/kg/day there were no maternal effects and no effects in the offspring on sexual maturation, neurobehavioral or reproductive function parameters in the rat offspring. At these doses, no drug-related evidence of teratogenic potential was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E 460(i))
Mannitol (E 421)
Croscarmellose sodium (E 468)
Hydroxypropylcellulose (E 463)
Sodium laurilsulfate
Magnesium stearate (E 470b)

Film coating

Macrogol poly(vinyl alcohol) grafted copolymer (E 1209)
Talc (E 553b)
Titanium dioxide (E 171)
Glycerol mono and dicaprylocaprate (E 471)
Poly(vinyl alcohol) (E 1203)
Indigo carmine aluminum lake (E 132)
Carmine (E 120)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

Polyvinylchloride (PVC)/Aluminium foil blister containing 14 film-coated tablets.

Pack sizes of 14, 28 or 98 tablets.

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

Cytokinetics (Ireland) Limited
45 Mespil Rd.
Dublin D04 W2F1
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/25/2014/001-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 February 2026

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

Cytokinetics (Ireland) Limited
45 Mespil Rd.
Dublin D04 W2F1
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 marketing authorisation holder (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 aficamten in each Member State, the Marketing Authorisation Holder (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 the important potential risk of heart failure due to systolic dysfunction and embryo-foetal toxicity.

The MAH shall ensure that in each Member State where aficamten is marketed, all HCPs who prescribe aficamten have access to/are provided with the Healthcare Professional Information Pack which contains:

- Information on where to find the latest Summary of Product Characteristics (SmPC)
- HCP Checklist
- Patient Card

A statement with "▼ This medicinal product is subject to additional monitoring" will be included on all educational materials together with instructions for reporting adverse reactions.

The HCP checklist will contain the following messages:

Before starting treatment with aficamten

For patients of childbearing potential:

- Advise the patient of the potential risk of embryo-foetal toxicity associated with aficamten and the need for further monitoring (foetal echocardiography) in case of pregnancy.
- Counsel on the need to avoid pregnancy and the need for an effective form of contraception during treatment with MYQORZO.
- Discuss benefit-risk considerations of treatment during pregnancy and the need for regular monitoring (e.g. every 2 weeks) of foetal cardiac function during pregnancy.
- Instruct the patient that they must inform their doctor immediately if they are pregnant, think they may be pregnant or planning to become pregnant.

For all patients:

- Ensure patient's LVEF is ≥ 55% on recent assessment.
- Inform the patient of the potential risk of systolic dysfunction leading to heart failure during treatment with aficamten and that they must consult their doctor or seek medical attention immediately if they experience new or worsening arrythmia, dyspnoea, chest pain, fatigue or leg oedema.
- Check that the patient is not currently planning on taking fluconazole or rifampicin while taking aficamten.
- Assess for potential interactions. Ask if the patient is on stable treatment with CYP2C9 inhibitors, or a CYP2C9 or CYP3A inducer as per the SmPC sections 4.2, 4.4 and 4.5.
- Advise the patient not to start, stop, or change any medicinal product without consulting the prescriber.
- Advise the patient to take aficamten as prescribed and advise the patient of what to do in the case of a missed dose or overdose.
- Highlight the Patient Card in each package

During treatment at each clinical visit (as described in the SmPC)

For patients of childbearing potential:

- Remind patients of the potential risk of embryo-foetal toxicity associated with aficamten and the need for further monitoring (foetal echocardiography) in case of pregnancy.
- Remind women of childbearing potential to use effective contraception during treatment.
- Advise the patient that they must inform their doctor if they are pregnant or planning to become pregnant and in case of pregnancy the need for regular monitoring (e.g. every 2 weeks) of foetal cardiac functions.
- Ensure the patient is closely monitored; consider foetal echocardiography to monitor for signs of foetal cardiac dysfunction.

For all patients:

- Assess the patient for signs, symptoms, and clinical findings of heart failure per the guidance provided in the SmPC section 4.4.

- Perform an echocardiogram to assess LVEF (as per frequency stated in SmPC section 4.2) and a Valsalva LVOT-G and maintain, adjust or withhold aficamten treatment as per section 4.2 of the SmPC.
- Assess for serious illness (e.g. severe infection), new arrhythmia (e.g. new or uncontrolled atrial fibrillation or other uncontrolled tachyarrhythmia), assess for worsening systolic function.
- Remind the patient they must consult their doctor or seek medical attention immediately if they experience new or worsening arrhythmia, dyspnoea, chest pain, fatigue, or leg oedema.
- Check if the patient plans to start a CYP2C9 inhibitor or discontinue CYP2C9 or CYP3A inducer and adjust dose as per section 4.2 of the SmPC.
- Advise the patient not to start, stop, or change any medicinal product without consulting the prescriber.
- Advise the patient to take aficamten as prescribed and advise the patient of what to do in the case of a missed dose or overdose.

The Patient Card which will be part of the Annex IIIa of Product Information, will contain the following key messages:

For patients of childbearing potential:

- The effects of MYQORZO on an unborn child are not fully known.
- Women of childbearing potential need to use effective form of contraception during treatment.
- Tell your doctor immediately if you are pregnant, think you may be pregnant or plan to become pregnant.
- Your doctor will discuss with you the potential risks of taking this medicine during pregnancy and decide if the treatment should be started or continued.
- If you are treated with MYQORZO during pregnancy, your doctor will carefully monitor you and your baby's heart function by doing echocardiograms. If there is a change in you or your baby's heart function, your doctor may adjust your dose or stop the treatment.

For all patients:

- Instruction to carry the Patient Card all the time and to show it to any HCP who sees the patient.
- Statement that aficamten is indicated for the treatment of symptomatic obstructive hypertrophic cardiomyopathy.
- Information about the potential risk of heart failure due to systolic dysfunction.
- Information that is it important to have echocardiogram appointments because the doctor needs to check the effect of MYQORZO on the heart.
- Instruction to tell the doctor straight away if the patient experiences new or worsening irregular heartbeat shortness of breath, chest pain, tiredness, leg swelling, or serious infection.
- Instruction not to start, stop or change any medicine without consulting the prescriber of aficamten.
- Contact details of the prescriber.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

MYQORZO 5 mg film-coated tablets
aficamten

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 5 mg aficamten.

3. LIST OF EXCIPIENTS

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
14 tablets
28 tablets
98 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
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

Store below 30 °C.

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

Cytokinetics (Ireland) Limited
45 Mespil Road
Dublin D04 W2F1
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/25/2014/005 (Pack size of 14 tablets)
EU/1/25/2014/001 (Pack size of 28 tablets)
EU/1/25/2014/009 (Pack size of 98 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MYQORZO 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

MYQORZO 5 mg tablets
aficamten

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Cytokinetics

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

MYQORZO 10 mg film-coated tablets
aficamten

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 10 mg aficamten.

3. LIST OF EXCIPIENTS

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
14 tablets
28 tablets
98 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
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

Store below 30 °C.

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

Cytokinetics (Ireland) Limited
45 Mespil Road
Dublin D04 W2F1
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/25/2014/006 (Pack size of 14 tablets)
EU/1/25/2014/002 (Pack size of 28 tablets)
EU/1/25/2014/010 (Pack size of 98 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MYQORZO 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

MYQORZO 10 mg tablets
aficamten

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Cytokinetics

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

MYQORZO 15 mg film-coated tablets
aficamten

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 15 mg aficamten.

3. LIST OF EXCIPIENTS

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
14 tablets
28 tablets
98 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
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

Store below 30 °C.

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

Cytokinetics (Ireland) Limited
45 Mespil Road
Dublin D04 W2F1
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/25/2014/007 (Pack size of 14 tablets)
EU/1/25/2014/003 (Pack size of 28 tablets)
EU/1/25/2014/011 (Pack size of 98 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MYQORZO 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

MYQORZO 15 mg tablets
aficamten

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Cytokinetics

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

MYQORZO 20 mg film-coated tablets
aficamten

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 20 mg aficamten.

3. LIST OF EXCIPIENTS

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
14 tablets
28 tablets
98 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
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

Store below 30 °C.

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

Cytokinetics (Ireland) Limited
45 Mespil Road
Dublin D04 W2F1
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/25/2014/008 (Pack size of 14 tablets)
EU/1/25/2014/004 (Pack size of 28 tablets)
EU/1/25/2014/012 (Pack size of 98 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MYQORZO 20 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

MYQORZO 20 mg tablets
aficamten

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Cytokinetics

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

CONTENT OF PATIENT CARD

PATIENT CARD

MYQORZO®▼
(aficamten)

Patient instructions: Carry this card with you **at all times**. Tell any healthcare professional who sees you that you are taking aficamten and show this card to them.

Aficamten is indicated for the treatment of obstructive hypertrophic cardiomyopathy. Refer to the package leaflet for more information or contact *[insert local contact details]*.

Safety information for patients of childbearing potential:
- *The effects of MYQORZO on an unborn baby are not fully known.*
- Women of childbearing potential have to use effective contraception during treatment.
- You should not use this medicine while pregnant unless your doctor evaluates your condition and prescribes it for you.
- Tell your doctor immediately if you are pregnant, think you may be pregnant or plan to become pregnant.
- Your doctor will discuss with you the potential risks of taking this medicine during pregnancy and decide if the treatment should be started or continued.
- If you are treated with MYQORZO during pregnancy, your doctor will carefully monitor you and your baby's heart function by doing echocardiograms. If there is a change in you or your baby's heart function, your doctor may adjust your dose or stop the treatment.

Safety information for all patients:
- Although not observed in clinical studies, aficamten may increase your risk of heart failure due to systolic dysfunction, a condition where the heart cannot pump with enough force and which can be life-threatening.
- It is very important to have echocardiogram appointments, because your doctor needs to check the effect of MYQORZO on your heart.
- Tell your doctor or pharmacist **immediately** if you experience new or worsening irregular heartbeat (arrhythmia), shortness of breath, chest pain, tiredness, leg swelling or serious infection.
- Do not start, stop or change any medication without consulting your prescriber of aficamten.

Please complete this section or ask your prescriber of aficamten to complete it.

Patient's name:_____
Name of prescriber: _____
Office phone number: _____
After-hours phone number: _____
Hospital name (if applicable): _____

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects that you may experience to *[add local reporting number/mail/address etc. here]*.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

MYQORZO 5 mg film-coated tablets
MYQORZO 10 mg film-coated tablets
MYQORZO 15 mg film-coated tablets
MYQORZO 20 mg film-coated tablets
aficamten

▼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.
- You will receive **a Patient Card**. Read it carefully and follow the instructions.
- Always show the Patient Card to the doctor, pharmacist, or nurse when you see them or if you go to the hospital.
- If you have any further questions, ask your doctor.
- 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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What MYQORZO is and what it is used for

MYQORZO contains the active substance aficamten. Aficamten is a reversible cardiac myosin inhibitor, meaning that it changes the action of the muscle protein myosin in heart muscle cells.

MYQORZO is used to treat adults with a type of heart disease called obstructive hypertrophic cardiomyopathy (oHCM). It is used in adults who have symptoms of the disease (class II or class III oHCM). The ‘class’ reflects the seriousness of the disease: ‘class II’ involves slight limitation of physical activity and ‘class III’ involves marked limitation of physical activity.

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 leaving the heart and can also make the heart muscle stiff. This blockage (obstruction) makes it harder for blood to enter and exit the heart, reducing its ability to pump blood to the rest of the body. This condition is known as obstructive hypertrophic cardiomyopathy (oHCM). Symptoms of oHCM include chest pain and shortness of breath (especially with physical exercise), tiredness, abnormal heart rhythms, dizziness, feeling you are about to faint, fainting (syncope) and swelling of the ankles, feet, legs, abdomen and/or veins in the neck.

The active substance in MYQORZO, aficamten, binds to the protein myosin in the heart muscle. This reduces the excess contraction of the heart which helps the heart pump more smoothly, reduces the blockage in blood flow and may improve symptoms of oHCM.

2. What you need to know before you take MYQORZO

Do not take MYQORZO:
- if you are allergic to aficamten or any of the other ingredients of this medicine (listed in section 6).
- If you are taking the following medicines:
  - fluconazole for more than 1 dose (a medicine commonly used to treat fungal infections).
  - adagrasib (a medicine used for the treatment of certain cancers).
  - rifampicin (an antibiotic for infections like tuberculosis).
  - St. John's wort (an herbal supplement for depression).

Ask your doctor if the medicine you are taking prevents you from taking aficamten. See section 'Other medicines and MYQORZO'.

Do not take MYQORZO if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking MYQORZO.

Warnings and precautions
Talk to your doctor before taking MYQORZO.

Tell your doctor or pharmacist immediately if you get any of these symptoms (new or worsening) during your treatment with MYQORZO:
- irregular heartbeats (arrhythmia)
- shortness of breath (dyspnoea)
- chest pain
- tiredness 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 (see section 4).

Tell your doctor or pharmacist immediately if you develop a serious infection or new or worsening irregular heartbeat (arrhythmia) as this could increase your risk of developing systolic dysfunction and heart failure. Your doctor may need to do additional tests to evaluate how well your heart is functioning.

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) to check your left ventricular ejection fraction (LVEF; the amount of blood pumped out of the heart by the lower left chamber in one beat). This will be done before your first dose and regularly during treatment with MYQORZO. It is very important to have these echocardiogram appointments, because your doctor needs to check the effect of MYQORZO on your heart. Your treatment dose may need to be adjusted to improve your response or to reduce side effects.

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

Other medicines and MYQORZO
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 MYQORZO works. Some medicines can increase the amount of MYQORZO 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 MYQORZO in your body and may reduce its beneficial effects.

Do not take MYQORZO if you are taking any of the following:
- more than 1 dose of fluconazole (a medicine used to treat fungal infections)
- adagrasib (a medicine used to treat certain types of cancer)

- rifampicin (an antibiotic for infections like tuberculosis)
- St. John's wort (an herbal supplement for depression)

Before taking MYQORZO 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 treat fungal infections, for example voriconazole
- Medicines used to treat certain anxiety disorders, for example fluvoxamine, fluoxetine
- Some medicines used to treat bacterial infections, for example sulfaphenazole
- Medicines used to treat cancer, such as apalutamide, enzalutamide, mitotane
- Some medicines used to treat seizures, for example carbamazepine, phenytoin

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 MYQORZO, 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 MYQORZO.

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 MYQORZO in your body.

Pregnancy

Women of childbearing potential have to use effective contraception during treatment.

There is no experience of using MYQORZO in pregnant women. It is uncertain if MYQORZO could cause harm to your unborn baby. You should not use this medicine while pregnant unless your doctor evaluates your condition and prescribes it for you. If you are pregnant, think you may be pregnant or are planning to become pregnant tell your doctor immediately. Your doctor will discuss with you the potential risks of taking MYQORZO during pregnancy and decide if the treatment should be started or continued. If you are treated with MYQORZO during pregnancy, your doctor will carefully monitor you and your baby's heart function by doing echocardiograms. If there is a change in you or your baby's heart function, your doctor may adjust your dose or stop the treatment.

Breast-feeding
If you plan to breast feed, ask your doctor or pharmacist for advice before taking this medicine. This is because it is not known whether the medicine passes into human breast milk or what the effects might be on the baby.

Driving and using machines
MYQORZO 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 (see section 4 'Possible side effects').

MYQORZO contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take MYQORZO

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Treatment with MYQORZO should be started under the supervision of a doctor experienced in the management of patients with cardiomyopathy.

Your doctor will prescribe you a single daily dose of either 5 mg, 10 mg, 15 mg or 20 mg. The maximum single dose is 20 mg once daily.

The recommended starting dose is one 5 mg film-coated tablet taken by mouth once a day. After you start treatment, your doctor will increase your dose by 5 mg every 2 to 8 weeks until a regular daily (maintenance) dose or the maximum daily dose is reached.

Your doctor will tell you how much MYQORZO to take.

Echocardiograms
While you are taking MYQORZO, your doctor will monitor how well your heart is working using echocardiograms and may adjust your dose based on the results of your echocardiogram (increase or lower your dose or temporarily stop treatment).

Your first echocardiogram will be done before you start treatment, and then again during follow-up visits every 2 to 8 weeks to assess how you are responding to MYQORZO. If your doctor changes your dose of MYQORZO at any point, an echocardiogram will be performed within 8 weeks afterwards to make sure you are receiving the correct dose (see section 2, Routine tests). When you have reached a regular daily (maintenance) dose, echocardiograms will be done every 3 months or 6 months.

Taking this medicine
Swallow the tablet whole with a glass of water each day. Do not split, crush, or chew the tablet. You can take this medicine with or without food.

If you take more MYQORZO than you should
If you take more tablets than you should, contact your doctor or go to a hospital immediately. If possible, take the medicine pack and this leaflet with you.

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

If you stop taking MYQORZO
Do not stop taking MYQORZO unless your doctor tells you to. If you stop taking MYQORZO, your HCM symptoms may return. If you wish to stop taking MYQORZO, 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 MYQORZO:

Common (may affect up to 1 in 10 people)
- dizziness
- new or worsening shortness of breath, chest pain, tiredness, 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.
- feeling your heartbeat.
- increase in blood pressure.

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 MYQORZO

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 pack after 'EXP'. The expiry date refers to the last day of that month.

Store below 30 °C.

Do not throw away any medicines via wastewater. 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 MYQORZO contains
- The active substance is aficamten. Each film-coated tablet (tablet) contains 5 mg, 10 mg, 15 mg or 20 mg aficamten.

- The other ingredients are:
  - Tablet core: Microcrystalline cellulose (E 460), mannitol (E 421), croscarmellose sodium (E 468), hydroxypropylcellulose (E 463), sodium laurilsulfate, magnesium stearate (E 470b). See section 2 'MYQORZO contains sodium'.
  - Tablet film coating: Macrogol poly (vinyl alcohol) grafted copolymer (E 1209), talc (E 553b), titanium dioxide (E 171), glycerol mono and dicaprylocaprate (E 471), poly (vinyl alcohol) (E 1203), indigo carmine aluminium lake (E 132), carmine (E 120).

What MYQORZO looks like and contents of the pack
- MYQORZO 5 mg film-coated tablets are purple, round tablets debossed with "5" on one side and "CK" on the other side. Tablet size of approximately 4.84 mm in diameter.
- MYQORZO 10 mg film-coated tablets are purple, triangle tablets debossed with "10" on one side and "CK" on the other side. Tablet size of approximately 6.73 mm x 6.99 mm.
- MYQORZO 15 mg film-coated tablets are purple, pentagon tablets debossed with "15" on one side and "CK" on the other side. Tablet size of approximately 7.33 mm x 7.37 mm.
- MYQORZO 20 mg film-coated tablets are purple, oval tablets debossed with "20" on one side and "CK" on the other side**.** Tablet size of approximately 5.46 mm x 10.29 mm.

The tablets are available in aluminium foil blisters containing 14 film-coated tablets.

Each pack contains 14, 28 or 98 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder
Cytokinetics (Ireland) Limited
45 Mespil Road
Dublin D04 WF21
Ireland
Tel: +353 1 200 3014
medinfo.europe@cytokinetics.com

Manufacturer
Cytokinetics (Ireland) Limited
45 Mespil Rd.

Dublin D04 W2F1
Ireland

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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.