CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Center for Drug Evaluation and Research
Division of Cardiology and Nephrology

NDA 214998 Interim CDTL Review Preceding Major Amendment for REMS Revision

DATE:	11/15/2021
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PROCUCT NAME:	Mavacamten (Camzyo)
PRODUCT CLASS:	Negative Myosin Modulator
SPONSOR:	Myokardia/BMS

Interim CDTL Executive Summary of Regulatory Status Through 11/10/2021, The Time of Submission of a REMS Revision That Was Considered a Major Amendment

Disease State Background

Sarcomeric hypertrophic cardiomyopathy (HCM) is a common autosomal dominant genetic heart disease that affects men and women globally.[1] The prevalence of unexplained asymptomatic hypertrophy among young adults in the United states has been estimated at 1/200 to 1/500, with symptomatic hypertrophy based medical claims data being less common (estimated at (b) (4)). The diagnosis of this condition is made from imaging that demonstrates a maximal end-diastolic wall thickness of at least 15 mm anywhere in the left ventricle in the absence of another cause for hypertrophy in adults. When present in family members of a subject known to have HCM or in subjects with a positive genetic test, wall thicknesses of at least 13 mm can be diagnostic as well. Variants is 1 of 8 genes coding for sarcomere-related structures have been identified as potentially causal, with more than 1500 recognized variants of these genes. However,

[1] Ommen SR et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020;76(25):e159-e240

among patients with HCM, only 30-60% have an identifiable pathologic variant. Commonly associated structural abnormalities including abnormally small intramural coronary arteries, elongated mitral valve leaflets, and congenital anomalies of the sub-mitral valve apparatus have no known direct association with sarcomere variants. Left ventricular outflow tract obstruction (LVOTO) occurs in approximately 75% of subjects, especially when the hypertrophic muscle mass involves the anterobasal cardiac septum. Mitral regurgitation occurs frequently, caused either by systolic anterior motion of the anterior mitral leaflet as a result of Bernoulli forces, or associated abnormalities of the mitral valve. Diastolic ventricular compliance is reduced, sometimes markedly so. Atrial fibrillation in these subjects is common.

The severity of HCM varies dramatically with respect to clinical symptomatology and natural history. Many subjects remain asymptomatic throughout their lives and enjoy a normal life expectancy. Others suffer varying degrees of symptoms, most frequently shortness of breath, chest pain, and palpitations. Some of these symptoms are secondary to a chronic relative ischemia in the setting of high muscle mass but relatively sparse coronary vasculature to supply that mass. HCM-related adverse outcomes include sudden death events, progressively limiting symptoms caused by diastolic dysfunction and/or LVOTO, heart failure (HF) caused by systolic dysfunction, and thromboembolic complications of atrial fibrillation.

Approved and Guideline-Directed Medical and Surgical Therapies

Propranolol is approved for the treatment of HCM subjects to improve NYHA class based on an uncontrolled series of 13 subjects. Non-dihydropyridine calcium channel blockers and disopyramide are guide-line directed but off-label medical therapies for this condition as well. For those suffering or at risk for the above-noted HCM-related adverse outcomes, contemporary cardiovascular (CV) therapies to include ICD implantation for those at high risk for sudden cardiac death (SCD) have lowered the annual mortality rate to less than 1% per year, with the occurrence of HF now being the predominant cause of disease-related morbidity and mortality. For those with severe LVOTO and symptoms refractory to guideline-directed medical therapy (GDMT), septal reduction therapy with surgical myectomy, or alcohol septal ablation for those at high surgical risk, can confer important symptomatic relief.

EXPLORER-HCM Efficacy and Integrated Safety

In the Phase 3 trial EXPLORER-HCM, mavacamten was administered to adults with obstructive HCM (oHCM) whose baseline ejection fraction was at least 55%, with a peak LVOT gradient of at least 50 mmHg as assessed by echocardiography at rest, after Valsalva maneuver, or post-exercise (confirmed by echocardiography core laboratory interpretation), an LVOT gradient of at least 30 mmHg with Valsalva maneuver, and NYHA class II or III symptoms at screening. Monotherapy with beta-blockers, verapamil, or diltiazem was allowed. Concomitant therapy with beta-blocker with diltiazem or beta-blocker with verapamil was excluded, as was monotherapy with disopyramide or ranolazine. Prior treatment with cardiotoxic agents such as doxorubicin

was likewise excluded. The primary efficacy endpoint of the trial was the proportion of subjects achieving either 1) An improvement of at least 1.5 mL/kg/min in peak oxygen consumption (pVO2) as determined by cardiopulmonary exercise testing (CPET) and a reduction of one or more class in NYHA Functional Classification or 2) an improvement of 3.0 mL/kg/min or more in pVO2 with no worsening in NYHA Functional Class. Secondary endpoints that were evaluated within the confines of an alpha-sparring hierarchy included the change from baseline to Week 30 in post-exercise LVOT peak gradient, the proportion of participants with at least 1 class improvement in NYHA functional class from baseline to Week 30, the change from baseline to Week 30 in (pVO2) as determined by CPET, the change from baseline to Week 30 in participant-reported health-related quality of life as assessed by the KCCQ score, and the change from baseline to Week 30 in patient-reported severity of HCM symptoms as assessed by the HCM Symptom Questionnaire score. All of these endpoints favored mavacamten therapy with high statistical significance, with FDA results verifying what was reported by the sponsor (see section 5.3 of the clinical review).

However, during extended follow-up, eight serious adverse events of heart failure (HF) occurred in mavacamten-treated subjects, as compared to only one such event in a placebo-treated subject, per the table below:

EXPLORER-HCM (PK/PD Monitoring)				MAVA-LTE[2] (EXPLORER Cohort, PD monitoring)		ISS[2] oHCM+nHCM	
Mavacamten (N=123) n (%)		Placebo (N=128) n (%)		Mavacamten (N=231) n (%)		Mavacamten (N=314) n (%)	
n (%)	ER (per 100 pt-yrs)	n (%)	ER (per 100 pt-yrs)	n (%)	ER (per 100 pt-yrs)	n (%)	ER (per 100 pt-yrs)
1 (0.8)	1.14	1 (0.8)	1.09	5 (2.2)[2]	1.99	8 (2.5)	1.70

1. Cardiac failure SAE was defined as any SAE of cardiac failure (SMQ, narrow), systolic dysfunction (preferred term) or any LVEF ≤ 30% from hospital, local or central lab.
2.Using updated safety data through May 2021 (section 7.6.12)
Source: Reviewer's Table

Benefit-Risk Assessment

The Number Needed to Treat (NNT) was calculated per the following table:

Mavacamten (N=123)		**Placebo (N=128)**	
Achieved Composite Functional Endpoint n (%)	Did not Achieve Composite Functional Endpoint n (%)	Achieved Composite Functional Endpoint n (%)	Did not Achieve Composite Functional Endpoint n (%)
45 (36.6)	78 (63.4)	22 (17.2)	106 (82.8)

NNT=1/(0.828-0.634)=5.2

The Number Needed to Harm (NNH) was defined as the occurrence of cardiac failure/systolic dysfunction SAE or LVEF ≤30% calculated per the following table:

	Mavacamten (N= 341)	**Placebo (N = 147)**	**Risk Difference (95% CI)**	**NNH**
Cardiac failure/systolic dysfunction SAE or LVEF ≤ 30%	8 (2.5%)[1]	1 (0.7%)	1.8 (-0.4, 4.0)	55

1. Two cases were associated with LVOT-G data-entry error; RD is 1.1 (-0.9, 3.1) and NNH = 91 excluding the 2 cases

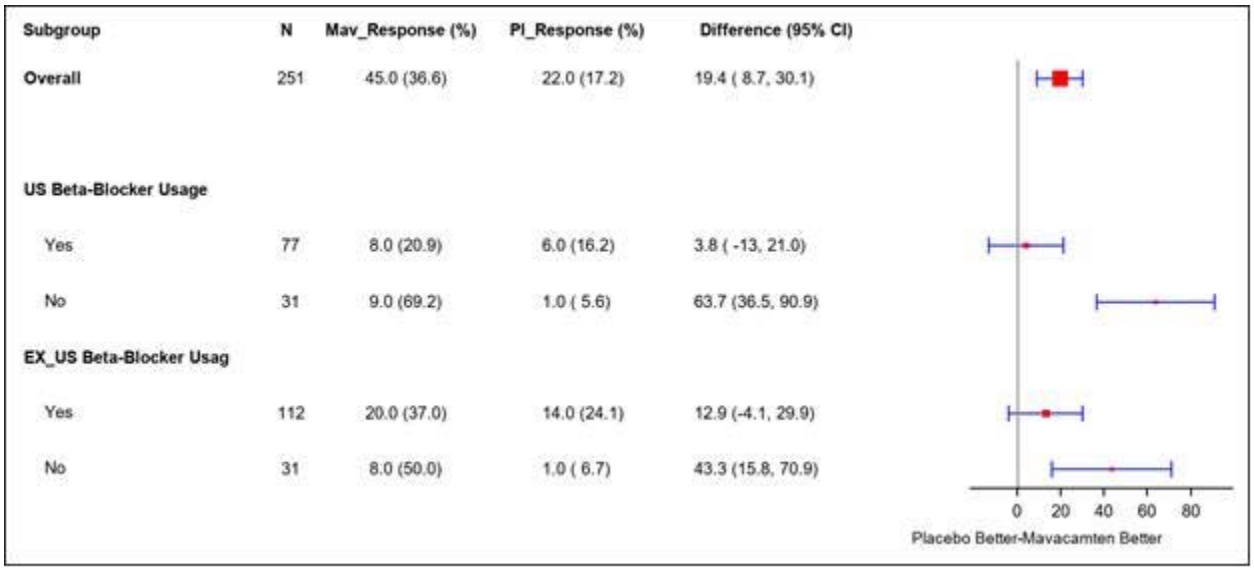
From these data, the review team concluded that:

- NNT = 5
- NNH = 55
- For every 55 patients treated, 11 will achieve clinical improvement of the efficacy primary outcomes, and 1 person will experience an SAE of HF or LVEF <30%
- The "real world" NNH outside of a tightly controlled clinical trial may be lower
- Among intermediate-slow CYP2C19 metabolizers, the NNH may be lower with current dosing algorithm
- The clinical team noted that two cases of SAE HF occurred as the direct result of inappropriate dosing caused by echocardiography interpretation errors
- The clinical team had concerns about potential drug-drug interactions (DDIs) as a result of CYP2C19 polymorphisms and consulted with clinical pharmacology to define this risk (see DDI subsection below).

Lack of Efficacy on a Background of Beta-blocker Therapy

For the primary efficacy endpoint of EXPLORER-HCM, there was a statistically significant interaction with background beta-blocker therapy, showing a lack of efficacy in beta-blocked subjects, as seen in the analysis below (FDA Biometrics):

Figure 3 Subgroup Analysis of Primary Endpoint by Beta-Blocker Usage



Statistically Significant but Small Absolute Improvements in Components of Efficacy

For the components of efficacy that were measured as continuous functions, the treatment effect size was approximately equal to or smaller than the estimate of within subject variability for those parameters, as shown in the table below (FDA Biometrics):

Within Subject Variability of Continuous Variables from EXPLORER-HCM

Variable	Estimate of Within-Subject Variability	Treatment Effect
PVO2 (mL/kg/min)	3.0	1.4
LVOT (mmHg)	-29.6	-35
NYHA class	-	-
KCCQ	10.1	9.1
HCMSQ	-1.7	-1.8

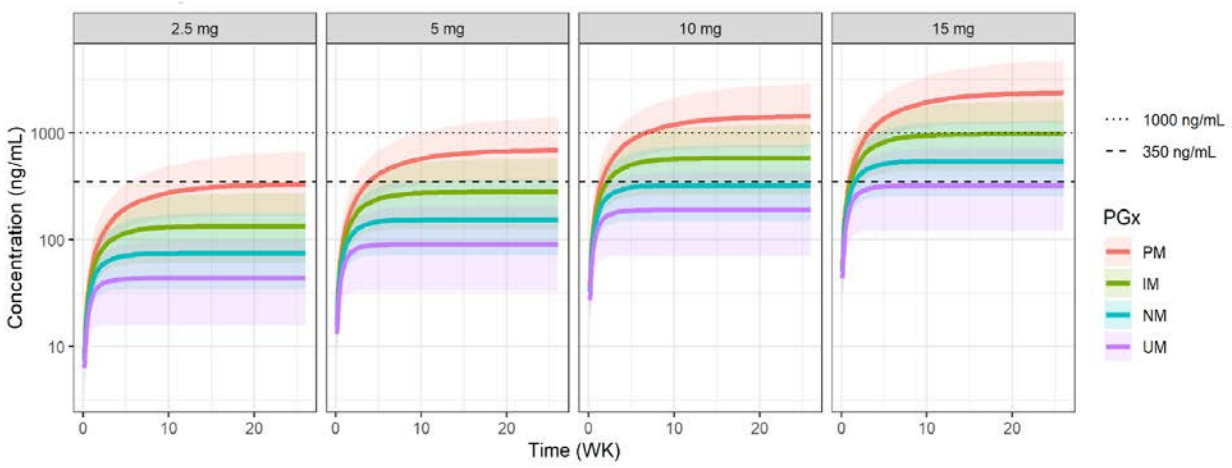
Excessive On-target Pharmacology, Toxicokinetics, and Elimination

See the Clinical Pharmacology Review.

Mavacamten has demonstrated a steep concentration to pharmacodynamic (LVEF) relationship in preclinical models. Both rat and dog studies demonstrated mavacamten's very narrow therapeutic index, with a mere 3-fold safety margin between the NOAEL and mortality. Death of a 10 month old human infant has recently occurred following accidental ingestion of three 15mg mavacamten pills. This child's drug-induced electromechanical dissociation was refractory to intravenous pressors, ECMO, dialysis, and attempts at CYP2C19 induction with rifampin. It is because of mavacamten's narrow therapeutic index that its toxicokinetic and ADME attributes become more problematic. Specifically,

- Mavacamten is extensively metabolized (CYP2C19: ~74%; CYP3A4: ~18%; and CYP2C9: ~8%).
- Exposure of the most abundant metabolite MYK-1078 is <4% of the exposure of mavacamten.
- Total radioactivity ~7% (1% as unchanged) in feces and ~85% (3% as unchanged) in urine.
- Mavacamten has a long half-life in normal CYP2C19 metabolizers (~7 days) which becomes dramatically longer in CYP2C19 poor metabolizers (~23 days).
- Dose adjustments are necessary for the coadministration of both CYP2C19 inhibitors and CYP3A4 inhibitors.

Population PK modeling demonstrated the considerable impact of differing CYP2C19 genotypes on mavacamten exposure, with an approximately 3.5-fold higher AUC in poor metabolizers (PMs) as compared to normal metabolizers (NMs). The Pop-PK model-predicted time-course of mavacamten trough concentrations in oHCM are shown below for PMs, intermediate metabolizers (IMs), NMs, and ultra-rapid metabolizers (UMs) (FDA Clinical Pharmacology):



Sequential USPI Posology Proposals

Following the exposure-response simulations of outcomes that were requested by the Division, the sponsor proposed the following posology modification:

	Initially Proposed USPI Posology	Proposed Modified USPI Posology
Starting Dose	5 mg	5 mg
Temporary Discontinuation*	LVEF < 50%	**LVEF** (b) (4)
Down-Titration	Week 4 if VLVOT < 20 mmHg → 2.5 mg QD	(b) (4)
Up-Titration	Week 12 if LVEF ≥ 55% & VLVOT ≥ 30 mmHg	Week 12 if LVEF ≥ 55% & VLVOT ≥ 30 mmHg

* Following temporary discontinuation, restart at a lower dose if the LVEF criterion to restart therapy is met.
Note: Changes in the proposed modified USPI posology compared to the initially proposed USPI posology are shown in bold.

About this, in our 9/30/2021 DRL, the Division stated the following:

- Minimizing safety risks based on CYP2C19 genotype during use is critical. Accordingly, available data including modeling and simulations indicate that prospective CYP2C19 genotyping and the availability of a companion diagnostic may be required for optimizing therapeutic use of mavacamten.
- For the CYP2C19 genotype-based DDI management strategy, there is a lack of information to provide appropriate dosing recommendations for CYP2C19 intermediate metabolizers co-administered with CYP2C19 and CYP3A inhibitors and for CYP2C19 normal metabolizers who are co-administered with a moderate CYP2C19 inhibitor.
- Even with appropriate identification of subjects at risk of high drug exposure and adverse reactions with prospective CYP2C19 genotyping, there is an inherent risk from inadvertent DDIs (e.g. OTC use of CYP2C19 inhibitors) that are difficult to control in clinical use.
- According to your simulation clinical scenario #N3, CYP2C19 poor metabolizers would be at 2-3 times the risk of other patient sub-groups for mavacamten-induced deterioration of left ventricular function that would mandate dose interruption and/or discontinuation for a period of approximately 30 weeks.
- We have concerns about the application of exposure-response models to predict LVEF measurements based on the recently proposed modified USPI posology in section 1.2.4.1 of the IR response submitted on 9/7/2021, because the proposed modified USPI posology includes a dosing regimen and ECHO-guided dose adjustment criteria that are significantly different from the pivotal study - EXPLORER-HCM.
- Your proposed new posology is complex, untested, and would require an equally complex REMS in an attempt to assure the safe use of mavacamten
- It is not appropriate for (b) (4)

With the preparation of the Late Cycle Meeting Package dated 10/21/2021, the Division commented further as follows:

- Please refer to our midcycle communication dated July 29, 2021. In that communication, we expressed our concern that eight serious cases of mavacamten-induced heart failure and/or systolic dysfunction occurred in the integrated summary of safety (ISS) data through May 2021. One of these serious heart failure/systolic dysfunction SUSARs (suspected unexpected serious adverse reactions) occurred in a subject who had been on a stable dose of mavacamten therapy for a period of approximately one year prior to clinical decompensation. The Division also expressed concern regarding the finding from the population PK (popPK) analysis that CYP2C19 PMs demonstrated decreased mavacamten clearance.
- We were concerned that "intercurrent medical events" that were thought to be contributors to important mavacamten-induced deterioration of ventricular systolic function (both left and right) were poorly defined. It was noted that multiple subjects experiencing serious heart failure experienced large elevations of NTpro-BNP prior to or at the time of their SUSAR heart failure events, both in the presence and in the absence of AFib/AFlutter. This raised the question as to whether rising NT-pro-BNP levels predict the occurrence of serious heart failure, and thus whether NT-pro-BNP levels should be checked at the time of echocardiography in follow-up.
- The Division was also concerned that slow accumulation by less than normal CYP2C19 metabolizers could result in a poor and/or intermediate metabolizer being inappropriately up-titrated early in the course of mavacamten therapy, thereby relying on subsequent echocardiography to reduce and/or hold mavacamten dosing based on the demonstration of mavacamten-induced deterioration of left ventricular systolic function (no assessments of mavacamten's impact on right ventricular function are incorporated into its dosing algorithm).
- Subsequently, simulations that you performed based on the popPK and exposure-response (E-R) models that you submitted to the NDA confirmed these concerns. In addition to (but related to) this issue of serious mavacamten-induced deterioration of left and/or right ventricular systolic function, the Division also raised the following concerns (please also refer to the Discipline Review Letter dated September 30, 2021):
    - Your proposed modified labeling posology includes ECHO-guided dose adjustment criteria that are significantly different from the pivotal study (EXPLORER-HCM). In addition, the Division is not convinced that a REMS could be constructed that would incorporate the added complexity of the newly-proposed posology (shown in the table above), (b) (4)

(b) (4)

- Mavacamten is extensively metabolized (CYP2C19: ~74%; CYP3A4: ~18%; and CYP2C9: ~8%). In less than normal CYP2C19 metabolizers, CYP3A4 assumes increasing importance in the clearance of mavacamten. Exposure of the most abundant metabolite MYK-1078 is <4% of the exposure of mavacamten. Radiolabeled excretion evaluation demonstrates total radioactivity ~7% (1% as unchanged) in feces and ~85% (3% as unchanged) in urine. Mavacamten's terminal half-life is 6 to 9 days in CYP2C19 normal metabolizers, versus 23 days in CYP2C19 poor metabolizers.

(b) (4)

(b) (4)

About this, the Division is currently not in agreement (b) (4)

NDA 214998

PBPK Modeling of Drug-Drug Interactions (DDIs)

FDA conducted physiologically based pharmacokinetic (PBPK) analyses to evaluate the effects of fluconazole (a strong CYP2C19 and moderate CYP3A inhibitor), ketoconazole (a strong CYP3A inhibitor), diltiazem (a moderate CYP3A inhibitor), rifampin (a strong CYP3A and CYP2C19 inducer), and efavirenz (a moderate CYP3A and CYP2C19 inducer) on the PK of mavacamten in subjects with various CYP2C19 phenotypes. Based on fold changes in C_{trough} (trough concentration at steady state), the following table demonstrates FDA's current assessment of mavacamten dose adjustments that will be necessary as a function of CYP2C19 phenotype and exposures to modulators of CYP2C19 and CYP3A:

Table 1-2 Dose Adjustment of Mavacamten during its Concomitant Administration with CYP Modulators

Perpetrators		CYP2C19 Phenotype	Current Mavacamten Dose (mg)			
			2.5	5	10	15
CYP2C19 Inhibitors	Strong	Non-PM†	Avoid			
	Moderate*	Non-PM†	Avoid			
	Weak	Non-PM†	Avoid	Reduce (to 2.5 mg)	Reduce (to 7.5 mg)	Reduce (to 10 mg)
CYP3A Inhibitors	Strong	NM, RM, UM	Avoid	Reduce (to 2.5 mg)	Reduce (to 7.5 mg)	Reduce (to 10 mg)
		PM, IM	Avoid	Reduce (to 2.5 mg)	Reduce (to 5 mg)	Reduce (to 7.5 mg)
	Moderate	NM, RM, UM	No Dose Adjustment			Reduce (to 12.5 mg)
		PM, IM	Avoid	Reduce (to 2.5 mg)	Reduce (to 5 mg)	Reduce (to 7.5 mg)
CYP3A & CYP2C19 Inducers	Strong	All	Avoid			
	Moderate	All	Up titration+	Up titration+	Avoid	Avoid

+Up titration not to exceed 15 mg daily dose; †Non-PM includes IM, NM, RM and UM of CYP2C19.
**No information is available on the effects of moderate inhibitors of CYP2C19.*

About this, the Division provided the following comments to the sponsor in our Late Cycle Meeting Package:

(b) (4)

[redacted]

Companion Diagnostic

The following comments were provided to the sponsor in the Late Cycle Meeting Package:

- It is unclear that current FDA-cleared CYP2C19 tests would be adequate to serve as a companion diagnostic test to support the proposed use of mavacamten. The following genotypes are important to be included in testing: CYP2C19 *1/*1, *2/*2, *2/*3, *3/*3, *1/*2, *1/*3, *2/*17, *3/*17, *1/*17 and *17/*17.

In follow-up, our CDRH consultant stated the following:

- Per the Companion Diagnostic Devices guidance, a companion diagnostic device is defined as “an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.” If this device would be essential for the safe and effective use of mavacamten, then it would be considered a companion diagnostic.

- The relevant alleles for mavacamten dosing would be CYP2C19 *1, *2, *3 and *17, to help identify normal, poor, intermediate, rapid and ultrarapid metabolizers.
- There are several in vitro diagnostics that are currently FDA cleared for detection of these CYP2C19 variants, such as the Spartan RX CYP2C19 Test System (k123891), the Verigine® CYP2C19 Nucleic Acid Test (CYP2C19) (k120466), and the Infiniti CYP2C19 Assay (k101683). However, while these devices are indicated for identifying *2, *3, and *17 alleles, these devices are not intended for establishing differential dosage and monitoring regimen.
- The accuracy of presently cleared 510(k) assays in determining rare CYP2C19 variants is supported by a very limited number of samples, and sometimes only a single measurement was used to support the accuracy of detection (for example, *3/*3 and *3/*17).
- Therefore the confidence in the assay to measure this genotype is nil.
- It may be possible for the drug sponsor to collaborate with the manufacturer of an existing 510(k) device such that companion diagnostic claims (to support the safe and effective dosing of mavacamten) could be added to a presently marketed CYP2C19 assay. However, additional validation studies (e.g., a more robust accuracy study with better confidence) may be needed to support such claims for a presently cleared 510(k) assay.
- When a therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device, it may be appropriate to approve a therapeutic product even if an IVD companion diagnostic device is not yet approved or cleared.

In response to the last bulleted statement, this reviewer communicated to our CDRH consultant that EXPLORER-HCM did not measure irreversible morbidity or mortality. It demonstrated highly statistically significant improvements in measures of function and quality of life that were small in magnitude relative to the intra-subject variability of those measures. Therefore, waiving the requirement for a companion device does not seem justified based on that criterion.

REMS

An extensively revised REMS was submitted to FDA for review on 11/8/2021. This has been deemed a major amendment and has not yet been reviewed.

Overdosage

About overdose, the current USPI states only the following:

- Human experience of overdose with [TRADENAME] is limited. [TRADENAME] has been given as a single dose of up to 144 mg in patients with

HCM. (b) (4) In healthy subjects, doses of up to 25 mg have been administered for up to 25 days, with 3 of 8 participants treated at the 25 mg dose level experiencing 20% or greater reductions in LVEF.

- Systolic dysfunction is the most likely result of overdosage of [TRADENAME]. (b) (4) treatment of overdose with [TRADENAME] consists of discontinuation of [TRADENAME] (b) (4) as well as medically supportive measures to maintain hemodynamic (b) (4) including close monitoring of vital signs and LVEF and management of the clinical status of the patient.

About death, the current USPI states only the following:

(b) (4)

What is not communicated is the details of the accidental ingestion of three pills of 15mg mavacamten by a 10 month old who within 90 minutes deteriorated to electromechanical dissociation that was refractory to intravenous pressors, dialysis, ECMO, and attempts at CYP2C19 with rifampin. This infant was pronounced dead approximately 48 hours after the ingestion. This case was submitted to the IND for mavacamten. Unlike what is currently fairly benign-sounding and non-specific direction that is currently given in the overdose section of the label, this case is informative in that it demonstrates the importance of understanding the narrow therapeutic window of this drug. It demonstrates that human subjects may reach an exposure past which the excess pharmacology of mavacamten is life-threatening and non-responsive to pressors and dialysis. Those facts are not communicated in the current overdose section of the label.

Indication Statement

The sponsor seeks an indication "For the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms." However, given the difficulties that will be associated with the administration of this drug if it is approved, it is the opinion of this CDTL that the indication statement should reflect the fact that its efficacy was confined for the most part to subjects not on background beta blockers. Likewise, it is unknown if all genetic

variants of sarcomeric HCM have a hypercontractile phenotype. For those that may not, administering mavacamten has a less compelling rationale. Therefore, it is also the opinion of this CDTL that the indication statement should reflect the minimal LVEF that was required for entry into EXPLORER-HCM (55%). Therefore, if approved, a reasonable indication statement could read as follows:

Mavacamten is indicated for the treatment of obstructive hypertrophic cardiomyopathy in patients with a baseline left ventricular ejection fraction of at least 55% who are persistently symptomatic through maximally tolerated doses of beta blockers, or who cannot take beta blockers.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PRESTON M DUNNMON
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