CYP2C19: mavacamten 7744 to 7746

AUC = area under the concentration-time curve, IM = intermediate metaboliser (*1/*2, *1/*3, *17/*2, *17/*3) (reduced CYP2C19 enzyme activity), NM = normal metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), NS = non-significant, PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP2C19 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, $t_{1/2}$ = half-life, UM = ultrarapid metaboliser (*17/*17) (elevated CYP2C19 enzyme activity)

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

Brief summary and justification of choices:
Mavacamten is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4.
The SmPCs indicate the mavacamten AUC to be 3.4 times higher in patients with gene variants leading to absent CYP2C19 activity (CYP2C19 poor metabolisers (PM)) than in patients with gene variants leading to normal CYP-2C19 activity (CYP2C19 normal metabolisers (NM)), indicating the presence of a CYP2C19-mavacamten interaction. In general, the KNMP Pharmacogenetics Working Group only provides therapeutic recommendations if clinical effects have been found or if the drug has a narrow therapeutic range. However, the SmPC indicates that the higher mavacamten exposure in PM can lead to increased risk of systolic dysfunction, i.e. heart failure, compared to NM. In addition, a reduction of the left ventricle ejection fraction (LVEF) by 20% or greater was experienced in 3 out of 8 healthy subjects treated with 25 mg mavacamten (i.e. 1.67-fold the registered maximum dose) for up to 25 days. So, while there is not enough evidence for clinical effects of the increased mavacamten exposure in PM, there is not enough evidence to reject it either. For this reason, the KNMP Pharmacogenetics Working Group decided to adopt the pharmacotherapeutic recommendation in the Dutch SmPC of mavacamten for PM (yes/yes-interaction).
The Dutch SmPC indicates that the effect on mavacamten exposure in IM and UM is smaller and clinically not relevant. Accordingly, the KNMP Pharmacogenetics Working Group decided not to provide a therapeutic recommendation for these two phenotypes (yes/ no-interactions).
You can find an overview of the kinetic effects per phenotype in the background information text of the gene-drug interaction in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

Recommendation concerning pre-emptive genotyping, including justification of choices:
Due to the absence of new clinical studies or case reports with patients with a CYP2C19 genotype leading to reduced or increased CYP2C19 activity in medical journals, and thus the absence of evidence of an increase in adverse events code ≥ D (grade ≥ 3) in these patients, the clinical implication of the gene-drug interaction scores only 2 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the Clinical Implication Score tables at the end of this risk analysis). However, there is not enough evidence to reject the warnings and recommendations in the SmPC. In addition, the Clinical Implication Score is mainly (for 80%) based on studies published in medical journals and therefore not suited to determine the clinical implication for gene-drug interactions for which data are only provided by pre-registration studies. For these reasons, the KNMP Pharmacogenetics Working Group decided to ignore the Clinical Implication Score and adopt the genotyping recommendation in the SmPC. The SmPC indicates that genotyping must be performed before starting mavacamten to guide dose selection. This would amount to genotyping being essential for drug safety according to the nomenclature of the KNMP Pharmacogenetics Working Group.

The table below uses the KNMP nomenclature for NM, PM, IM and UM. As a result, the definitions of NM, PM, IM and UM in the table below can differ from the definitions used by the authors in the reference.

Source	Code	Effect	Comments
ref. 1	3	12 healthy volunteers received a single dose of mavacamten	

<table>
<tr>
<td>Perera V et al. Effects of omeprazole and verapamil on the pharmacokinetics, safety, and tolerability of mavacamten: two drug-drug interaction studies in healthy participants. Clin Pharmacol Drug Dev 2023 Sep 28 (online ahead of print).. PMID: 37771180.

ref. 1, continuation</td>
<td>2
PM: AA</td>
<td>25 mg and 13 healthy volunteers received a a single dose of mavacamten 25 mg combined with the moderate CYP3A4 inhibitor verapamil (240 mg sustained release once daily on day 1-28). One of the volunteers in the mavacamten/verapamil group (either a NM or an IM) did not complete the study and was excluded from the pharmacokinetic analysis.
Given the low number of PM in the study, no statistical analysis of pharmacokinetic parameters was performed in PM.

Genotyping:
mavacamten only
- 11x NM
- 1x PM

mavacamten/verapamil
- 7x NM
- 4x IM
- 2x PM

Results:
<table>
<tr><td colspan="3">Results compared to NM (mavacamten only) or NM+IM (mavacamten/verapamil):</td></tr>
<tr><td></td><td>PM</td><td>value for NM or for NM+IM</td></tr>
<tr><td colspan="3">Mavacamten only</td></tr>
<tr><td>$AUC_{0-\infty}$</td><td>x 6,50 (NS)</td><td>17,220 ng.h/mL</td></tr>
<tr><td>adverse events</td><td colspan="2">There were no moderately severe or serious adverse events.</td></tr>
<tr><td colspan="3">Mavacamten/verapamil</td></tr>
<tr><td>$AUC_{0-\infty}$</td><td>x 2.42 (NS)</td><td>20,740 ng.h/mL</td></tr>
<tr><td>adverse events</td><td>There were no moderately severe or serious adverse events.</td><td>There was one moderately severe adverse event: presyncope leading to discontinuation from the study.</td></tr>
</table>
</td>
<td>AUC compared to NM:
PM: 650%</td>
</tr>
<tr>
<td>ref. 2
SmPC Camzyos (mavacamten) 07-08-23.</td>
<td>0</td>
<td><u>Dosing</u>:
Patients should be genotyped for Cytochrome P450 (CYP) 2C19 (CYP2C19) in order to determine appropriate mavacamten dose. Patients with CYP2C19 poor metabolizer phenotype may have increased mavacamten exposures (up to 3 times) that can lead to increased risk of systolic dysfunction compared to normal metabolizers. If treatment initiation occurs prior to determination of CYP2C19 phenotype, patients should follow dosing instructions for poor metabolisers until CYP2C19 phenotype is determined.
CYP2C19 poor metaboliser phenotype
The recommended starting dose is 2.5 mg orally once daily. The maximum dose is 5 mg once daily.
CYP2C19 intermediate, normal, rapid and ultra-rapid metaboliser phenotype
The recommended starting dose is 5 mg orally once daily. The maximum dose is 15 mg once daily.
Dose modification with concomitant medicinal products
For concomitant treatment with inhibitors and inducers of CYP2C19 or CYP3A4, follow the steps shown in table 1.

Table 1: Dose modification of mavacamten with concomitant medicinal products
<table>
<tr><td>Concomitant medicinal product</td><td>CYP2C19 poor metaboliser phenotype</td><td>CYP2C19 intermediate, normal, rapid and ultra-</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

ref. 2, continuation				rapid phenotype	
		Inhibitors			
		Combined use of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor	Contra-indicated.	Contra-indicated.	
		Strong CYP2C19 inhibitor (e.g., ticlopidine, fluconazole, fluvoxamine)	No dose adjustment.	Initiate mavacamten at a dose of 2.5 mg. The dose should be reduced from 15 mg to 5 mg and from 10 mg and 5 mg to 2.5 mg or pause treatment if on 2.5 mg.	
		Strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole, ketoconazole, voriconazole, ritonavir, cobicistat, ceritinib, idelalisib, tucatinib)	Contra-indicated.	No dose adjustment.	
		Moderate CYP-2C19 inhibitor (e.g., fluconazole, fluoxetine, omeprazole[a])	No dose adjustment.	No adjustment of the starting dose of 5 mg is needed. The dose should be reduced by one dose level or pause treatment if on 2.5 mg.	
		Moderate (e.g., erythromycin, grapefruit juice, verapamil, diltiazem) or weak (e.g., cimetidine, esomeprazole, omeprazole, pantoprazole) CYP3A4 inhibitor	No adjustment of the starting dose of 2.5 mg is needed. If patients are receiving a 5 mg dose of mavacamten, their dose should be reduced to 2.5 mg.	No dose adjustment.	
		Inducers			
		Discontinuing or decreasing the dose of strong CYP2C19 inducer and strong CYP-3A4 inducer (e.g., rifampicin, apalutamide, enzalutamide, mitotane, phenytoin, carbamazepine, efavirenz, St. John's wort)	The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg.	The dose should be reduced by one dose level when on doses 5 mg or higher when discontinuing or decreasing the dose of strong inducers while on mavacamten. No dose adjustment when on 2.5 mg.	
		Discontinuing or decreasing the dose of moderate	Decrease mavacamten dose to 2.5 mg or pause treat-	No dose adjustment.	

ref. 2, continuation		or weak CYP3A4 inducer (e.g., phenobarbital, primidone)	ment if on 2.5 mg.	

[a] Omeprazole is considered a weak CYP2C19 inhibitor at a dose of 20 mg once daily and a moderate CYP2C19 inhibitor at a total daily dose of 40 mg.

Contraindications:
Concomitant treatment with strong CYP3A4 inhibitors in patients with CYP2C19 poor metaboliser phenotype.
Warnings:
Heart failure risk or loss of response to mavacamten due to interactions
Mavacamten is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4 and mostly by CYP3A4 in CYP-2C19 poor metabolisers.
Prior to and during mavacamten treatment, the potential for interactions, including over the counter medicinal products, should be considered.
- Concomitant treatment with strong CYP3A4 inhibitors in patients with CYP2C19 poor metaboliser phenotype and undetermined CYP2C19 phenotype is contraindicated.

Interactions:
In CYP2C19 intermediate, normal, rapid and ultra-rapid metabolisers, mavacamten is primarily metabolised by CYP-2C19 and to a lesser extent by CYP3A4. In CYP2C19 poor metabolisers, metabolism is mostly by CYP3A4. CYP2C19 inhibitors/inducers and CYP3A4 inhibitors/inducers may thus affect the clearance of mavacamten and increase/decrease mavacamten plasma concentration, and this will depend on the CYP2C19 phenotype.
All clinical drug-drug interaction studies mainly enrolled CYP2C19 normal metabolisers and no CYP2C19 poor metabolisers were included in the assessment of the drug-drug interaction and therefore the effect of co-administration of CYP2C19 and CYP3A4 inhibitors with mavacamten in CYP2C19 poor metabolisers is not completely certain.
Recommendations for dose modification of patients initiating or discontinuing treatment with, or changing the dose of, concomitant medicinal products that are inhibitors of CYP-2C19 or CYP3A4 or inducers of CYP2C19 or CYP3A4 are provided in table 1.
Fertility, pregnancy and lactation:
Women of childbearing potential must use effective contraception during treatment and for 6 months after discontinuation of Camzyos, since it takes approximately 5 half-lives (approximately 45 days for CYP2C19 normal metabolisers and 115 days for CYP2C19 poor metabolisers) to eliminate mavacamten from the body after treatment discontinuation
Pharmacokinetics:
After a single dose of 15 mg mavacamten, C_{max} and AUC_{inf} are 47% and 241% higher, respectively, in CYP2C19 poor metabolisers compared to normal metabolisers. Mean half-life is prolonged in CYP2C19 poor metabolisers compared to normal metabolisers (23 days versus 6 to 9 days, respectively).
As mavacamten is titrated based on clinical response, simulated steady state exposures are summarized using individualised dosage by phenotype (table 2).

PM: A

AUC versus *1/*1:
PM: 341%

<table>
<tr>
<td>ref. 2, continuation</td>
<td>IM: AA
UM: AA</td>
<td>Table 2. Simulated average steady state concentration by dose and CYP2C19 phenotype in patients titrated to effect based on Valsalva LVOT and LVEF
<table>
<tr><td>Dose</td><td colspan="5">Median concentration (ng/ml)</td></tr>
<tr><td></td><td>Poor metabolisers</td><td>Intermediate metabolisers</td><td>Normal metabolisers</td><td>Rapid metabolisers</td><td>Ultra-rapid metabolisers</td></tr>
<tr><td>2.5 mg</td><td>451.9</td><td>274.0</td><td>204.9</td><td>211.3</td><td>188.3</td></tr>
<tr><td>5 mg</td><td>664.9</td><td>397.8</td><td>295.4</td><td>311.5</td><td>300.5</td></tr>
</table>
Mavacamten is extensively metabolised, primarily through CYP2C19 (74%), CYP3A4 (18%), and CYP2C9 (7.6%) based on in-vitro reaction phenotyping. Metabolism is expected to be driven through all three pathways, and primarily through CYP2C19 in CYP2C19 intermediate, normal, rapid and ultra-rapid metabolisers. In CYP2C19 poor metabolisers mavacamten is metabolised primarily by CYP-3A4. No data are available on the metabolite profile in CYP-2C19 poor metabolisers.
Terminal half-life is 6 to 9 days in CYP2C19 normal metabolisers and 23 days for CYP2C19 poor metabolisers.
Half-life is estimated to be, 6 days for CYP2C19 ultra-rapid metabolisers, 8 days for CYP2C19 rapid metabolisers, and 10 days for CYP2C19 intermediate metabolisers.
Drug accumulation occurs with an accumulation ratio about 2-fold for C_{max} and about 7-fold for AUC in CYP2C19 normal metabolisers. The accumulation depends on the metabolism status for CYP2C19 with the largest accumulation observed in CYP2C19 poor metabolisers.
CYP2C19 phenotype
Polymorphic CYP2C19 is the main enzyme involved in the metabolism of mavacamten. An individual carrying two normal function alleles is a CYP2C19 normal metaboliser (e.g., *1/*1). An individual carrying two non-functional alleles is a CYP2C19 poor metaboliser (e.g., *2/*2, *2/*3, *3/*3). The incidence of CYP2C19 poor metaboliser phenotype ranges from approximately 2% in Caucasian to 18% in Asian populations.
Exposure to mavacamten increased approximately dose proportionally between 2 mg and 48 mg and is expected to result in dose proportional exposure increase across the therapeutic range of 2.5 mg to 5 mg in CYP2C19 poor metabolisers and 2.5 mg to 15 mg in CYP2C19 intermediate to ultra-rapid metabolisers.</td>
<td>Simulated median concentration versus *1/*1:
PM: 221-225%
IM: 134-135%
UM: 92-102%</td>
</tr>
<tr>
<td>ref. 3
SmPC Camzyos (mavacamten), USA, 15-06-23.</td>
<td>0

PM: A

IM: AA</td>
<td><u>Pharmacokinetics</u>:
Mavacamten has a variable terminal $t_{1/2}$ that depends on CYP2C19 metabolic status.
Mavacamten terminal half-life is 6-9 days in CYP2C19 normal metabolizers (NMs), which is prolonged in CYP2C19 poor metabolizers (PMs) to 23 days. Drug accumulation occurs with an accumulation ratio of about 2-fold for C_{max} and about 7-fold for AUC in CYP2C19 NMs. The accumulation depends on the metabolism status for CYP2C19 with the largest accumulation observed in CYP2C19 PMs.
Moderate CYP3A4 Inhibitors:
Concomitant use of mavacamten (25 mg) with verapamil sustained release (240 mg) increased mavacamten AUC_{inf} by 16% and C_{max} by 52% in intermediate metabolizers (IMs; e.g., *1/*2, *1/*3, *2/*17, *3/*17) and NMs of CYP2C19.
Concomitant use of mavacamten with diltiazem in CYP2C19</td>
<td></td>
</tr>
</table>

ref. 3, continuation		PMs is predicted to increase mavacamten AUC_{0-24h} and C_{max} up to 55% and 42%, respectively. *Strong CYP2C19 and CYP3A4 Inducers:* Concomitant use of mavacamten (a single 15 mg dose) with a strong CYP2C19 and CYP3A4 inducer (rifampin 600 mg daily dose) is predicted to decrease mavacamten AUC_{0-inf} and C_{max} by 87% and 22%, respectively, in CYP2C19 NMs, and by 69% and 4%, respectively, in CYP2C19 PMs. <u>Pharmacogenomics</u>: Mavacamten AUC_{inf} increased by 241% and C_{max} increased by 47% in CYP2C19 poor metabolizers (PMs) compared to normal metabolizers (NMs) following a single dose of 15 mg mavacamten. Mean half-life is prolonged in CYP2C19 PMs compared to NMs (23 days vs. 6 to 9 days, respectively). Polymorphic CYP2C19 is the main enzyme involved in the metabolism of Camzyos. An individual carrying two normal function alleles is a NM (e.g., *1/*1). An individual carrying two no function alleles is a PM (e.g., *2/*2, *2/*3, *3/*3). The prevalence of CYP2C19 poor metabolizers differs depending on ancestry. Approximately 2% of individuals of European ancestry and 4% of individuals of African ancestry are PMs; the prevalence of PMs is higher in Asian populations (e.g., approximately 13% of East Asians).	AUC versus *1/*1: PM: 341%

Risk group	Strong CYP2C19 inhibitor usage by IM and UM patients, concomitant strong CYP2C19 inhibitor and strong CYP3A4 inhibitor usage by PM, IM and UM, strong CYP3A4 inhibitor usage by PM, moderate or weak CYP3A4 inhibitor usage by PM, discontinuation or dose reduction of strong CYP2C19 inducer and strong CYP3A4 inducer by PM, IM and UM, discontinuation or dose reduction of moderate or weak CYP3A4 inducer by PM

Comments:

- An article with information on the pharmacokinetic modelling underlying recommendations for different phenotypes in case of comedication in the SmPC was not included (Chiang M et al. Physiologically based pharmacokinetic modeling and simulation of mavacamten exposure with drug-drug interactions from CYP inducers and inhibitors by CYP2C19 phenotype. Clin Pharmacol Ther 2023;114:922-32. PMID: 37467157). The article only confirms that one of the two drug-drug interactions studies used in the modelling (mavacamten-omeprazole interaction) only investigated NM (*1/*1 and *1/*17) and that the other (mavacamten-verapamil interaction) investigated only 3 PM, and that given the low number of PM in this study, no statistical analysis of pharmacokinetic parameters was conducted for these participants. In addition, these data are also indicated in Perera 2023 (description of the mavacamten-omeprazole study not included in the risk analysis because only NM were investigated).

Date of literature search: 17 October 2023.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	PM	0 A	Yes	Yes	6 November 2023
	IM	0 AA	Yes	No	
	UM	0 AA	Yes	No	

Mechanism:
Mavacamten is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is	0-2 +

	available, the DPWG recommends adhering to the gene-drug guideline	
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	
OR		
• Recommendation to genotype	++	++
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	2+
Corresponding Clinical Implication Score:		Potentially beneficial
Score according to the SmPC:		Essential