Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)
Mavacamten (symptomatic (NYHA class II-III) obstructive hypertrophic cardiomyopathy)

of 1 February 2024

At its session on 1 February 2024, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Mavacamten as follows:

Mavacamten

Resolution of: 1 February 2024
Entry into force on: 1 February 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 26 June 2023):

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

Therapeutic indication of the resolution (resolution of 1 February 2024):

See therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III)

Appropriate comparator therapy:

- Therapy according to doctor's instructions, taking into account non-vasodilating beta-blockers, verapamil and diltiazem

Extent and probability of the additional benefit of mavacamten compared to the appropriate comparator therapy:

Hint for a considerable additional benefit.

Study results according to endpoints:[1]

Adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III)

1 Data from the dossier assessment of the IQWiG (A23-76) and from the addendum (A23-132), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	↑	Advantages in symptomatology (HCMSQ total score as well as PGIC and PGIS).
Health-related quality of life	↑	Advantages in health-related quality of life (KCCQ-OSS).
Side effects	↔	No relevant differences for the benefit assessment.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

EXPLORER-HCM study: RCT over 30 weeks; mavacamten versus placebo (in each case in addition to therapy according to doctor's instructions)

Mortality

Endpoint	Mavacamten + TDI		Placebo + TDI		Mavacamten + TDI vs placebo + TDI
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Overall mortality[a]	n.d.				

Morbidity

Endpoint	Mavacamten + TDI		Placebo + TDI		Mavacamten + TDI vs placebo + TDI
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Symptomatology					
PGIC[b]	102	87 (85.3)	88	47 (53.4)	1.62 [1.31; 2.00]; < 0.001[c]
PGIS[d]	98	53 (54.1)	86	32 (37.2)	1.54 [1.12; 2.12]; 0.008[c]

Endpoint	Mavacamten + TDI			Placebo + TDI			Mavacamten + TDI vs placebo + TDI
	N[e]	Values at start of study MV (SD)	Change at week 30 MV [95% CI];	N[e]	Values at start of study MV (SD)	Change at week 30 MV [95% CI];	MD [95% CI]; p value
Perceived exertion (RPE scale according to Borg)[f]	97	356.2 (38.0)	−8.3 [−14.7; −1.9][g]	88	352.4 (39.4)	2.6 [−4.1; 9.2][g]	−10.85 [−18.70; −3.01]; 0.007[g] SMD: −0.40 [−0.69; −0.11]
Symptomatology							
HCMSQ total score[i]	94	3.1 (1.5)	−1.3 [−1.6; −1.0][j]	82	2.9 (1.8)	−0.5 [−0.8; −0.1][j]	−0.87 [−1.25; −0.48]; < 0.001[j] SMD: −0.67 [−0.97; −0.37]
Shortness of breath	94	4.7 (2.5)	−2.3 [−2.8; −1.8][j]	82	4.3 (3.1)	−0.5 [−1.1; 0.0][j]	−1.75 [−2.43; −1.07][j]
Fatigue	94	1.3 (0.7)	−0.4 [−0.6; −0.3][j]	82	1.3 (0.8)	−0.2 [−0.4; −0.1][j]	−0.23 [−0.41; −0.05][j]
Cardiovascular symptoms	94	1.7 (1.5)	−0.8 [−1.1; −0.6][j]	82	1.7 (1.6)	−0.3 [−0.5; 0.0][j]	−0.57 [−0.88; −0.26][j]
Health status (EQ-5D VAS)[k]	89	70.5 (19.1)	9.0 [5.1; 12.9][j]	77	68.2 (19.8)	1.3 [−2.8; 5.5][j]	7.62 [2.55; 12.69]; 0.003[j] SMD: 0.46 [0.15; 0.77]

Health-related quality of life

Endpoint	Mavacamten + TDI			Placebo + TDI			Mavacamten + TDI vs placebo + TDI
	N[e]	Values at start of study MV (SD)	Change at week 30 MV [95% CI];	N[e]	Values at start of study MV (SD)	Change at week 30 MV [95% CI];	MD [95% CI]; p value
KCCQ-OSS[l]	87	67.6 (17.3)	15.0 [11.7; 18.3][j]	76	65.2 (19.7)	6.4 [3.0; 9.9][j]	8.58 [4.49; 12.66]; < 0.001[j] SMD: 0.64 [0.33; 0.96]
Physical limitation	87	71.2 (18.3)	13.0 [9.2; 16.7][j]	76	70.3 (19.6)	1.9 [−2.1; 5.8][j]	11.11 [6.34; 15.89][j]
Psychological quality of life	87	55.8 (23.7)	17.8 [13.4; 22.1][j]	76	54.4 (22.3)	9.0 [4.5: 13.5][j]	8.75 [3.31; 14.18][j]
Social limitation	87	72.1 (21.2)	14.5 [10.3; 18.6][j]	76	67.4 (24.5)	6.0 [1.6; 10.4][j]	8.47 [3.19; 13.74][j]
Symptoms (KCCQ-TSS)	87	71.4 (16.8)	12.8 [9.3; 16.2][j]	76	68.7 (21.8)	6.2 [2.6; 9.8][j]	6.56 [2.25; 10.87][j]

Side effects[m]

Endpoint	Mavacamten + TDI		Placebo + TDI		Mavacamten + TDI vs placebo + TDI
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
AE (presented additionally)	*110*	*99 (90)*	*100*	*83 (83)*	–
SAE	110	14 (12.7)	100	8 (8)	1.65 [0.70; 3.86]; 0.252[c]
Discontinuation due to AEs	110	2 (1.8)	100	1 (1)	1.94 [0.17; 22.18]; 0.594[c]
Systolic dysfunction (PT, SAE)[)n]	n.d.				

Endpoint	Mavacamten + TDI		Placebo + TDI		Mavacamten + TDI vs placebo + TDI
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value

a. The pharmaceutical company presents no data for the sub-population of patients who were treated according to the appropriate comparator therapy. In the total population, 1 event (0.8%) occurred in the control arm. Deaths were recorded as part of the survey on side effects.

b. Percentage of patients with any improvement ("very much improved", "much improved" or "slightly improved") at week 30

c. Mantel-Haenszel method with the stratification factors NYHA class (II vs III), concomitant oHCM therapy with beta blockers (yes vs no) and type of cardiopulmonary exercise test (treadmill vs cycle ergometer); 95% CI and p value based on normal distribution approximation

d. Percentage of patients with any improvement in symptom severity on a five-point scale ("no symptoms", "mild", "moderate", "severe" and "very severe") at week 30 compared to the start of study

e. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.

f. Patients rate their subjective perceived exertion during CPET every minute on the Borg RPE scale from 6 (no exertion at all) to 20 (maximal exertion) at the start of study and week 30. The area under the Borg scores results in a value range between 132 and 440. Lower (decreasing) values mean lower perceived exertion.

g. Covariance analysis adjusted for the value at the start of study and the stratification factors NYHA class (II vs III), concomitant oHCM therapy with beta blockers (yes vs no) and type of cardiopulmonary exercise test (treadmill vs cycle ergometer); MD represents the difference between the treatment arms in the changes from start of study to week 30.

h. Duration between start and regular end of CPET or premature discontinuation due to complete exhaustion or onset of clinical symptoms

i. Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 12.5).

j. MMRM adjusted for the value at the start of study and for the stratification factors NYHA class (II vs III), concomitant oHCM therapy with beta blockers (yes vs no) and type of cardiopulmonary exercise test (treadmill vs cycle ergometer); MD represents the difference between the treatment arms in the changes from the start of study to week 30.

k. Higher (increasing) values mean better health status; positive effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100).

l Higher (increasing) values mean a better health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100).

m. Side effects were recorded throughout the course of the study until week 38 (end of study).

n. The pharmaceutical company presents no data for the sub-population of patients who were treated according to the appropriate comparator therapy. In the total population, 1 event (0.8%) occurred in the intervention arm.

Abbreviations used: CPET: cardiopulmonary exercise test; HCMSQ: Hypertrophic Cardiomyopathy Symptom Questionnaire; oHCM: obstructive hypertrophic cardiomyopathy; n.d.: no data available; KCCQ: Kansas City Cardiomyopathy Questionnaire; CI: confidence interval; MD: mean difference; MMRM: mixed model for repeated measures; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; NYHA: New York Heart Association; OSS: overall summary score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: preferred term; RCT: randomised controlled trial; RPE: Received Perception of Exertion; RR: relative risk; SD: standard deviation; SMD: standardised mean difference; SAE: serious adverse event ; TDI: Therapy according to doctor's instructions; AE: adverse event; TSS: total symptom score; VAS: visual analogue scale

2. Number of patients or demarcation of patient groups eligible for treatment

Adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III)

approx. 18,900 – 19,500 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Camzyos (active ingredient: mavacamten) at the following publicly accessible link (last access: 17 October 2023):

https://www.ema.europa.eu/en/documents/product-information/camzyos-epar-product-information_en.pdf

Treatment with mavacamten should only be initiated and monitored by doctors experienced in cardiomyopathy therapy.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient card). In particular, the training material contains information and warnings on the risks of embryo-foetal toxicity, heart failure, possible interactions with other medicinal products and dose determination depending on the individual CYP2C19 phenotype.

Prior to initiating treatment with mavacamten, an echocardiogram must be performed and it must be confirmed that the patient's left ventricular ejection fraction (LVEF) is 55%.

In addition, patients must be genotyped for CYP2C19 in order to determine the patient-individual dosage of mavacamten. Patients capable of bearing children must have a negative pregnancy test prior to treatment.

4. Treatment costs

Annual treatment costs:

Adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed	
Mavacamten	€ 25,784.94
Additionally required SHI services	€ 170.19
Total	€ 25,955.13
Appropriate comparator therapy	
Therapy according to doctor's instructions, taking into account non-vasodilating beta-blockers, verapamil and diltiazem	
Non-vasodilating beta blockers	
Propranolol	€ 146.95 - € 245.86
Bisoprolol	€ 43.36 - € 50.22
Metoprolol	€ 40.15 - € 61.50
Atenolol	€ 52.82 - € 85.08
Betaxolol	€ 23.31 - € 46.61
Sotalol	€ 200.60
Calcium antagonists	
Verapamil	€ 135.78 - € 183.52
Diltiazem	€ 237.29 - € 271.93

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 January 2024

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III)

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 1 February 2024.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 1 February 2024

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken