Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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 obstructive hypertrophic cardiomyopathy (NYHA class II-III))

of 1 February 2024

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient mavacamten on 1 August 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 27 July 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 November 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of mavacamten compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of mavacamten.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Mavacamten (Camzyos) in accordance with the product information

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 the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for mavacamten:

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

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

on 1. Besides mavacamten, only the active ingredient propranolol is approved for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults.

on 2. In the present indication, no non-medical measures can be considered as the appropriate comparator therapy.

on 3. In the therapeutic indication to be considered here, there are no resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

The new active ingredient mavacamten is intended for the treatment of symptomatic oHCM in adults. In this therapeutic indication, only the active ingredient propranolol is approved in addition to the active ingredient mavacamten to be assessed.

Symptomatic oHCM is a severe, rare disease. There are no large, randomised studies available in this therapeutic indication. Overall, the evidence in the considered therapeutic indication is limited.

The AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy, 2020[2] was identified as a relevant guideline in the evidence search conducted as part of the determination of the appropriate comparator therapy. October 2023, a further guideline on the management of cardiomyopathies was published by the European Society of Cardiology (ESC)[3].

The AHA/ACC guideline on hypertrophic cardiomyopathy recommends with recommendation class 1 and evidence level B-NR (non-randomised studies) "In patients with obstructive HCM and symptoms attributable to LVOTO [left ventricular outflow tract obstruction], nonvasodilating beta-blockers, titrated to effectiveness or maximally tolerated doses". If these are insufficient or are not tolerated, the following therapy options are listed with recommendation class 1, evidence level B-NR for verapamil (non-randomised studies) or evidence level C-LD for diltiazem (limited data basis): "In patients with obstructive HCM and symptoms attributable to LVOTO, for whom beta-blockers are ineffective or not tolerated, substitution with non-dihydropyridine calcium channel blockers (e.g., verapamil, diltiazem) is recommended". These recommendations are underpinned by the new ESC guideline on cardiomyopathy.

Although in the product class of nonvasodilating beta-blockers only the active ingredient propranolol is explicitly approved in the indication to be assessed, the relevant guidelines recommend the product class of nonvasodilating beta-blockers overall.

Since β1-receptor-selective beta-blockers (e.g. bisoprolol, metoprolol) have a cardioselective effect, they are generally preferable in the present cardiovascular indication compared to non-selective beta-blockers in a relevant patient population for whom propranolol is unsuitable.

[2] 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy, https://www.ahajournals.org/doi/10.1161/CIR.0000000000000937
[3] 2023 ESC Guidelines for the management of cardiomyopathies, https://doi.org/10.1093/eurheartj/ehad194

In addition, not all patients covered by the therapeutic indication are eligible for treatment with a non-vasodilating beta-blocker, so that the lower-ranking recommendations of the guidelines are also taken into account for this patient population. Specifically, the calcium channel blockers verapamil and diltiazem are considered to be part of the therapy standard in the medical treatment situation in the event of non-response or contraindication to a beta-blocker.

The use of unapproved therapy options for relevant patient groups is therefore considered medically necessary for the severe and rare disease oHCM. In accordance with the generally recognised state of medical knowledge, it must be established overall that the off-label use of the above-mentioned therapy options for a relevant patient group is generally preferable to the active ingredient propranolol, which was previously approved in the therapeutic indication; Section 6, paragraph 2, sentence 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

In conclusion, the G-BA therefore comes to the conclusion that for adults with symptomatic obstructive hypertrophic cardiomyopathy, therapy according to doctor's instructions, taking into account nonvasodilating beta-blockers, verapamil and diltiazem, is the appropriate comparator therapy.

It is assumed that possible concomitant diseases are adequately treated.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

The determination of the off-label use of medicinal products as an appropriate comparator therapy by resolution on the benefit assessment according to Section 35a paragraph 3 SGB V does not affect the procedure according to Section 35c SGB V.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of mavacamten is assessed as follows:

For the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III), there is a hint for a considerable additional benefit for mavacamten compared with the appropriate comparator therapy.

Justification:

For the assessment of the additional benefit, the pharmaceutical company submits the results of the EXPLORER-HCM study.

The EXPLORER-HCM study is a double-blind, randomised controlled trial that enrolled a total of 251 adults with symptomatic oHCM (NYHA class II-III) with a left ventricular ejection fraction (LVEF) ≥ 55%. The study participants were randomised in a 1:1 ratio to the two study arms mavacamten (N = 123) versus placebo (N = 128). In both study arms, patient-individual, guideline-compliant medicinal concomitant therapy for oHCM was possible.

Patients with cardiovascular comorbidities (e.g. CHD, paroxysmal atrial fibrillation or 2nd degree atrioventricular block), but also patients with typical symptoms of oHCM (e.g. syncope and ventricular tachyarrhythmias) were not enrolled in the study due to the extensive inclusion and exclusion criteria.

The design of the study comprised a 30-week treatment phase followed by an 8-week follow-up phase without treatment with mavacamten or placebo. The primary endpoint of the study was the composite endpoint of clinical response. Furthermore, endpoints in the categories of morbidity, health-related quality of life and side effects were collected.

As part of the randomisation process, in addition to stratification according to concomitant oHCM therapy with beta-blockers (yes vs no), stratification according to NYHA class (II vs III), type of cardiopulmonary exercise test (treadmill vs bicycle ergometer) and consent to a magnetic resonance sub-study (yes vs no) was performed.

Relevant sub-population

For the present benefit assessment, only the results of the sub-population that received concomitant oHCM therapy according to the appropriate comparator therapy in the form of nonvasodilating beta-blockers, verapamil or diltiazem were considered (mavacamten N = 110, placebo N = 100). The EXPLORER-HCM study contains information on oHCM-specific concomitant therapies as well as information on all concomitant therapies. When forming the sub-population, the pharmaceutical company took into account those patients who received any concomitant therapy with one of the active ingredients corresponding to the appropriate comparator therapy. However, data from patients who received vasodilating beta-blockers, other calcium channel blockers or a combination therapy as concomitant treatment were not included in the benefit assessment.

According to the study protocol, adjustments to the oHCM concomitant therapy during the course of the study were only intended in the event of safety or tolerability concerns.

In the sub-population analysed, the percentage of subjects with a higher degree of physical limitation due to their heart disease (NYHA class III) was 25% in the intervention arm and 30% in the comparator arm. Data on how many of these patients simultaneously showed a left ventricular outflow tract (LVOT) gradient > 50 mmHg and would therefore have been eligible for invasive therapy according to the guideline recommendations are not available.

It is not clear from the study documents available for the benefit assessment how many study participants received a dosage regimen of mavacamten that conformed to the product information. Contrary to the requirements in the product information, there was no phenotype-related dosage regimen for mavacamten in the EXPLORER-HCM study. However,

this appears to be negligible, as only 2% of patients were slow CYPC19 metabolisers. In addition to the *left ventricular outflow tract (LVOT) gradient* and *LVEF* criteria specified in the product information, the *plasma concentration of mavacamten* was also used in the study for patient-individual dose adjustment. Furthermore, dose increases were already possible from week 8 in the study, whereas these are only planned from week 12 according to the product information.

Extent and probability of the additional benefit

Mortality

For the "overall mortality" endpoint, the pharmaceutical company does not provide data for the relevant sub-population treated according to the appropriate comparator therapy. In the total population, 1 death occurred in the comparator arm.

Morbidity

In the present assessment, morbidity is presented on the basis of perceived exertion (RPE scale according to Borg), symptomatology (HCMSQ total score as well as PGIC and PGIS) and health status (EQ-5D VAS).

Perceived exertion - using the Borg RPE scale

At the time of screening and at study week 30, cardiopulmonary exercise testing (CPET) was performed with increasing exercise on the treadmill or cycle ergometer with a connected electrocardiogram (ECG). Patients were asked to indicate their perceived exertion on a Borg RPE scale from 6 to 20 before and every minute during the examination (6: "no exertion", 20: "maximum exertion"). In the event of abnormal clinical symptoms or an abnormal ECG, early discontinuation by the study participants or the attending physician was possible.

Although the study protocol and the statistical analysis plan of the pharmaceutical company did not contain a pre-specification regarding the RPE scale according to Borg, the measurement instrument is considered suitable for recording the patient-relevant endpoint perceived exertion.

There was a statistically significant advantage of mavacamten over the appropriate comparator therapy for the "perceived exertion" endpoint. However, the 95%-confidence interval of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

The endpoint of maximum exertion time, which is also presented in the benefit assessment dossier, is not considered for the benefit assessment, as this was already included in the Borg RPE scale.

Symptomatology – using the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) total score

The HCMSQ is a questionnaire for collecting the oHCM-specific symptoms of shortness of breath, fatigue, palpitations, chest pain, dizziness and syncope. The patients themselves answer questions in the 3 domains of shortness of breath, fatigue and cardiovascular symptoms. For the HCMSQ total score, these domains are summarised as a weighted sum

(scale range: 0 to 12.5). Low values for this measurement instrument correspond to better symptomatology.

The results of the HCMSQ for collecting HOCM symptomatology show a statistically significant advantage of mavacamten compared to placebo, in each case in addition to therapy according to doctor's instructions. The effect is considered relevant because the 95% confidence interval of the standardised mean difference is completely outside the irrelevance range of -0.2 - 0.2.

Symptomatology – using Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS)

The PGIC consists of a single question to assess the overall change in symptom severity since the start of treatment. The assessment is made by the study participants on a 7-point scale with indications ranging from "very much improved" to "very much worse". For the present assessment, the results on the percentage of patients who assessed their health status at week 30 as "very much improved" or "much improved" or "minimally improved" compared to the start of treatment are used.

The PGIS also consists of only one question asking patients to rate their symptom severity within the last week on a 5-point scale ("no symptoms", "mild", "moderate", "severe" and "very severe"). The present benefit assessment takes into account the percentage of study participants who reported any improvement at week 30 compared to the start of study.

The evaluations of the PGIC and the PGIS at week 30 compared to the start of study each show statistically significant advantages of mavacamten along with therapy according to doctor's instructions compared to placebo along with therapy according to doctor's instructions.

Health status – using the visual analogue scale of the EQ-5D questionnaire (EQ-5D VAS)

Health status was assessed in the study using the EQ-5D VAS. Using EQ-5D VAS, the study participants rate their health status themselves on a scale from 0 (worst perceivable health status) to 100 (best perceivable health status).

A statistically significant advantage of mavacamten over placebo was observed for the health status endpoint, in each case along with therapy according to doctor's instructions. The 95% confidence interval of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

Composite endpoint of clinical response

The *clinical response* primary endpoint of the EXPLORER-HCM study is a combination of the components improvement in the value of the maximum oxygen uptake (pVO2) and improvement or stabilisation of the NYHA class. Laboratory parameters such as the pVO_2 value are categorised as not relevant to the patient if there is no evidence of their suitability as surrogate parameters. In addition, the classification according to NYHA primarily reflects the severity of the disease, so that secondary complications and symptoms are not adequately addressed.

Due to these limitations, the endpoint is not considered for the benefit assessment of mavacamten. Events in the endpoint categories of morbidity and health-related quality of life can be measured and shown directly via other patient-relevant endpoints.

Quality of life

The KCCQ questionnaire was used for the endpoint category of health-related quality of life.

Kansas City Cardiomyopathy Questionnaire - Overall Summary Score (KCCQ-OSS)

The KCCQ is a disease-specific questionnaire to assess health-related quality of life in patients with cardiomyopathy, which is completed by the study participants themselves. 6 domains are queried: physical limitations, symptoms (symptom frequency and severity), symptom stability, social impairment, self-efficacy, and quality of life. For evaluation, the items of the respective domains are summed up and transformed to a scale from 0 to 100. Higher values correspond to a better condition. The clinical summary score KCCQ-OSS is used for the early benefit assessment.

For the KCCQ-OSS, there is a statistically significant advantage of mavacamten over placebo, in each case along with therapy according to doctor's instructions. As the 95% confidence interval of the standardised mean difference lies outside the irrelevance range of -0.2 to 0.2, the effect is classified as relevant.

Side effects

SAEs

In the EXPLORER-HCM study, there was no statistically significant difference between the treatment groups in the evaluation of the endpoint of SAEs for the assessed population.

Discontinuation due to AEs

The results of the endpoint of discontinuation due to AEs show no statistically significant difference between mavacamten and placebo in each case along with therapy according to doctor's instructions.

Specific AEs

No separate data are available for the "Systolic dysfunction" (PT, SAEs) endpoint for the sub-population treated according to the appropriate comparator therapy. In the total population, 1 event was observed in the patient group treated with mavacamten.

Overall assessment

For the assessment of the additional benefit of mavacamten, evaluations of the double-blind, randomised, placebo-controlled phase III EXPLORER-HCM study (in each case along with therapy according to doctor's instructions) are available at week 30. To derive an additional benefit, the sub-population that received concomitant oHCM therapy according to the appropriate comparator therapy in the form of nonvasodilating beta-blockers, verapamil or diltiazem was considered.

In the endpoint category of mortality, no separate data are available for the sub-population treated according to the appropriate comparator therapy. In the total population, 1 death occurred in the comparator arm.

In the morbidity category, there were statistically significant advantages of mavacamten over the appropriate comparator therapy at study week 30 for the symptomatology endpoint (assessed using HCMDQ, PGIC and PGIS). There were no relevant advantages of mavacamten

for the endpoints of perceived exertion (measured using the Borg RPE scale) and health status (measured using the EQ-5D VAS).

In the category of health-related quality of life (assessed using the KCCQ-OSS), mavacamten also showed a statistically significant advantage over the appropriate comparator therapy .

In the side effects category, there were no statistically significant differences between the two treatment arms neither for serious adverse events nor discontinuations due to adverse events.

Overall, there were statistically significant advantages of mavacamten over the appropriate comparator therapy at week 30, both in the endpoint category of morbidity and in health-related quality of life, which were classified as considerable. These advantages are not offset by any disadvantages from other endpoint categories.

Against this background, a considerable additional benefit was derived for mavacamtem for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III) in adults compared with the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

This assessment is based on the results of the EXPLORER-HCM study, a randomised, double-blind, direct comparator phase III study.

The risk of bias at study level is rated as low. At the endpoint level, the risk of bias for the results on symptomatology (PGIC) and side effects is assessed as low. However, the high percentage of study participants not included in the evaluation leads to a high risk of bias for the endpoints of perceived exertion, symptomatology (HCMSQ and PGIS), health status and health-related quality of life.

Regardless of the low risk of bias at study level, there are uncertainties as to how many study participants received mavacamten in compliance with the marketing authorisation. In addition to the *LVOT gradient* and *LVEF* criteria specified in the product information, the *plasma concentration of mavacamten* was also taken into account for patient-individual dose adjustment. In addition, dose increases were already possible from week 8 in the study, whereas these are only planned from week 12 according to the product information.

There are also uncertainties as to whether the sub-population under consideration was optimally adjusted to the concomitant therapy at the start of the study and during the course of the study. For example, there is no information on whether all patients were on the maximum tolerated dose of beta-blockers at the start of the study, or whether patients who were receiving a calcium channel blocker at the start of study were intolerant of beta-blockers or not sufficiently effective. As the study medication could only be adjusted during the study if there were safety or tolerability concerns, it is unclear overall whether all patients received an optimally adjusted concomitant therapy during the course of the study.

Against the background of these uncertainties, the reliability of data is rated in the "hint" category.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Camzyos with the active ingredient mavacamten. Mavacamten is approved for the treatment of symptomatic (NYHA class II - III) obstructive hypertrophic cardiomyopathy (oHCM) in adults.

The G-BA determined the appropriate comparator therapy to be a therapy according to doctor's instructions, taking into account non-vasodilating beta-blockers, verapamil and diltiazem.

The double-blind, randomised, placebo-controlled phase III EXPLORER-HCM study (in each case along with therapy according to doctor's instructions) was used to assess the additional benefit of mavacamten. To derive an additional benefit, the sub-population that received concomitant oHCM therapy according to the appropriate comparator therapy in the form of nonvasodilating beta-blockers, verapamil or diltiazem was considered.

In the endpoint category of mortality, no data are available for the sub-population treated according to the appropriate comparator therapy. In the total population, 1 death occurred in the comparator arm.

In the morbidity category, there were statistically significant advantages of mavacamten over the appropriate comparator therapy for the symptomatology endpoint. There were no relevant advantages of mavacamten for the endpoints of perceived exertion and health status.

In the category of health-related quality of life, mavacamten also showed a statistically significant advantage over the appropriate comparator therapy.

In the side effects category, there were no statistically significant differences between the two treatment arms neither for serious adverse events nor discontinuations due to adverse events.

The statistically significant advantages of mavacamten over the appropriate comparator therapy in the endpoint categories of morbidity and health-related quality of life are not offset by any disadvantages from other endpoint categories.

The significance of the evidence is categorised as a hint, as there are uncertainties regarding the use of mavacamten in the study in compliance with the marketing authorisation and regarding the optimum setting of the concomitant therapy.

In the overall assessment, a hint for a considerable additional benefit of mavacamten compared to the appropriate comparator therapy is identified.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the patient numbers stated in the pharmaceutical company’s dossier.

The patient number estimated by the pharmaceutical company is subject to uncertainty overall. Among other things, the determination of sample sizes on the basis of several, partly

unspecific ICD codes for cardiomyopathy leads to both underestimated and overestimated factors in patient numbers. It is not possible to quantify the extent of these opposing effects. In addition, the suitability of the publication used to estimate the percentage of patients with NYHA class II and III is questionable due to a study population different from that of the target population.

Based on the assumption of increasing prevalence, it can be assumed that the sample sizes for the current year are higher than the estimates given, which are based on data from 2019.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2024).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower

available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

The active ingredients bisoprolol, sotalol, verapamil and diltiazem are not approved for this therapeutic indication. For cost representation, against the background of missing dosage information in the respective product information, the publications of Nistri S et al.[4], Dybro AM et al.[5], Tendera M et al.[6] and Elliott PM et al.[7] were used.

The active ingredients metoprolol tartrate, atenolol and betaxolol are also not approved for the indication in question. Dosage recommendations from the equivalence dosage tables for beta-blockers of the German Pharmacists' Drug Commission are used for cost representation[8].

The beta-blocker nadolol is currently not approved in Germany and is therefore not included in the cost representation.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Mavacamten	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Therapy according to doctor's instructions, taking into account non-vasodilating beta-blockers, verapamil and diltiazem				
Non-vasodilating beta blockers				
Propranolol	Continuously, 3 - 4 x day	365.0	1	365.0
Bisoprolol[4]	Continuously, 1 x daily	365.0	1	365.0
Metoprolol[8]	Continuously, 1 x daily	365.0	1	365.0
Atenolol[8]	Continuously, 1 x daily	365.0	1	365.0

[4] Nistri S et al., β Blockers for prevention of exercise-induced left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2012 Sep 1;110(5):715-9. doi: 10.1016/j.amjcard.2012.04.051. Epub 2012 May 24. PMID: 22633205.

[5] Dybro AM et al., Randomized Trial of Metoprolol in Patients With Obstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2021 Dec 21;78(25):2505-2517. doi: 10.1016/j.jacc.2021.07.065. PMID: 34915981.

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Betaxolol[8]	Continuously, 1 x daily	365.0	1	365.0
Sotalol[6]	Continuously, 1 x daily	365.0	1	365.0
Calcium antagonists				
Verapamil[7]	Continuously, 2 - 3 x day	365.0	1	365.0
Diltiazem[7]	Continuously, 2 - 3 x day	365.0	1	365.0

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Mavacamten	2.5 mg – 15 mg	2.5 mg – 15 mg	1 x 2.5 mg – 1 x 15 mg	365.0	365 x 2.5 mg – 365 x 15 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions, taking into account non-vasodilating beta-blockers, verapamil and diltiazem					
Non-vasodilating beta blockers					
Propranolol	10 mg – 40 mg	30 mg – 160 mg	3 x 10 mg – 4 x 40 mg	365.0	1,095 x 10 mg – 1,460 x 40 mg
Bisoprolol[4]	5 mg – 10 mg	5 mg – 10 mg	1 x 5 mg – 1 x 10 mg	365.0	365 x 5 mg – 365 x 10 mg
Metoprolol[8]	50 mg – 200 mg	50 mg – 200 mg	1 x 50 mg – 1 x 200 mg	365.0	365 x 50 mg – 365 x 200 mg
Atenolol[8]	25 mg – 100 mg	25 mg – 100 mg	1 x 25 mg – 1 x 100 mg	365.0	365 x 25 mg – 365 x 100 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Betaxolol[8]	10 mg – 20 mg	10 mg – 20 mg	0.5 x 20 mg – 1 x 20 mg	365.0	182.5 x 20 mg – 365 x 20 mg
Sotalol[6]	320 mg	320 mg	2 x 160 mg	365.0	730 x 160 mg
Calcium antagonists					
Verapamil[7]	40 mg – 240 mg	120 mg – 480 mg	3 x 40 mg – 2 x 240 mg	365.0	1,095 x 40 mg – 730 x 240 mg
Diltiazem[7]	60 mg – 180 mg	180 mg – 360 mg	3 x 60 mg – 2 x 180 mg	365.0	1,095 x 60 mg – 730 x 180 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Mavacamten 2.5 mg	98 HC	€ 7,341.04	€ 2.00	€ 415.96	€ 6,923.08
Mavacamten 15 mg	98 HC	€ 7,341.04	€ 2.00	€ 415.96	€ 6,923.08
Appropriate comparator therapy					
Propranolol 10 mg[9]	100 TAB	€ 15.77	€ 2.00	€ 0.35	€ 13.42
Propranolol 40 mg[9]	100 TAB	€ 19.49	€ 2.00	€ 0.65	€ 16.84
Bisoprolol 5 mg[9]	100 FCT	€ 14.10	€ 2.00	€ 0.22	€ 11.88
Bisoprolol 10 mg[9]	100 FCT	€ 16.14	€ 2.00	€ 0.38	€ 13.76
Metoprolol 50 mg[9]	100 TAB	€ 13.14	€ 2.00	€ 0.14	€ 11.00
Metoprolol 200 mg[9]	100 SRT	€ 19.50	€ 2.00	€ 0.65	€ 16.85

[9] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Atenolol 25 mg[9]	100 FCT	€ 16.91	€ 2.00	€ 0.44	€ 14.47
Atenolol 100 mg[9]	100 FCT	€ 26.51	€ 2.00	€ 1.20	€ 23.31
Betaxolol 20 mg[9]	100 FCT	€ 14.77	€ 2.00	€ 0.00	€ 12.77
Sotalol 160 mg	100 TAB	€ 31.04	€ 2.00	€ 1.56	€ 27.48
Verapamil 40 mg[9]	100 FCT	€ 14.67	€ 2.00	€ 0.27	€ 12.40
Verapamil 240 mg[9]	100 SRT	€ 28.50	€ 2.00	€ 1.36	€ 25.14
Diltiazem 60 mg[9]	100 TAB	€ 24.73	€ 2.00	€ 1.06	€ 21.67
Diltiazem 180 mg[9]	100 REC	€ 41.65	€ 2.00	€ 2.40	€ 37.25
Abbreviations: FCT = film-coated tablets; HC = hard capsules; TAB = tablets; SRT = sustained release tablet; SRC = sustained release capsules					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Determination of the left ventricular ejection fraction (LVEF) using echocardiography

Patients being treated with the active ingredient mavacamten should have their left ventricular ejection fraction (LVEF) determined by echocardiography prior to starting treatment.

CYP2C19 genotyping

Furthermore, costs are regularly incurred for the active ingredient mavacamten in accordance with the product information for carrying out CYP2C19 genotyping in order to determine the patient-individual dosage of mavacamten and to avoid an overdose.

Designation of the therapy	Designation of the service	Number	Cost per unit	Costs/ patient/ year
Medicinal product to be assessed:				

Designation of the therapy	Designation of the service	Number	Cost per unit	Costs/ patient/ year
Mavacamten	Determination of the left ventricular ejection fraction (LVEF) using echocardiography			
	Additional flat rate for cardiology (GOP: 13545)	1	€ 88.19	€ 88.19
	CYP2C19 genotyping			
	Genotyping to determine the CYP2C19 metabolic status prior to the administration of mavacamten in symptomatic (NYHA class II-III) oHCM (GOP: 32869)	1	€ 82.00	€ 82.00

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence

1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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.

References:
Product information for mavacamten (Camzyos); Camzyos hard capsules; last revised: June 2023

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 10 August 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 25 July 2023.

On 27 July 2023, the pharmaceutical company submitted a dossier for the benefit assessment of mavacamten to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 28 July 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient mavacamten.

The dossier assessment by the IQWiG was submitted to the G-BA on 24 October 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2023. The deadline for submitting written statements was 22 November 2023.

The oral hearing was held on 11 December 2023.

By letter dated 12 December 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 12 January 2024.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 23 January 2024, and the proposed resolution was approved.

At its session on 1 February 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 August 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	25 July 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	5 December 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 December 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 December 2023 16 January 2024	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	23 January 2024	Concluding discussion of the draft resolution
Plenum	1 February 2024	Adoption of the resolution on the Pharmaceuticals Directive

Berlin, 1 February 2024

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

Prof. Hecken