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 Vericiguat (chronic heart failure)

of 3 March 2022

Contents

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 first placing on the market of the active ingredient Vericiguat in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 September 2021. 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 14 September 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 December 2021 on the website of the G-BA (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 Vericiguat 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, the statements

submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. 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 Vericiguat.

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 Vericiguat (Verquvo) according to product information

Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilised after a recent decompensation event requiring IV therapy.

Therapeutic indication of the resolution (resolution of 3 March 2022):

see therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with symptomatic, chronic heart failure with reduced ejection fraction who are stabilised after a recent decompensation event requiring IV therapy

Appropriate comparator therapy for vericiguat:

An optimised standard therapy for the treatment of symptomatic chronic heart failure and underlying conditions such as hypertonia, arrhythmias, coronary heart disease, diabetes mellitus, hypercholesterolaemia and concomitant symptoms

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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 6.1 from 24.01.2022. 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 Federal Joint Committee has already determined the patient-relevant benefit 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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. The following active ingredients or active ingredients from the following product classes are generally approved for the treatment of heart failure:
- Angiotensin-converting enzyme inhibitors (ACE inhibitors): Captopril, cilazapril, enalapril, lisinopril, perindopril and ramipril
- AT1 receptor blockers (ARBs): Candesartan, losartan and valsartan
- Beta-adrenoceptor antagonists: Bisoprolol, carvedilol, metoprolol succinate and nebivolol
- Digitalis glycosides
- Diuretics: e.g. thiazides (hydrochlorothiazide)
- Mineralocorticoid receptor antagonists (MRAs): e.g. spironolactone, eplerenone
- Ivabradine
- Sacubitril/valsartan
- The SGLT-2 inhibitors dapagliflozin and empagliflozin

The following limitations apply: AT1 receptor blockers are only approved for the treatment of heart failure when angiotensin-converting enzyme (ACE) inhibitors are not tolerated or as add-on therapy to ACE inhibitors when appropriate. Beta-adrenoceptor antagonists are approved for the treatment of stable chronic mild to moderate heart failure with impaired systolic ventricular function (ejection fraction ≤ 40%), in addition to the usual standard therapy with ACE inhibitors and/or diuretics and, if necessary, digitalis glycosides. Digitalis glycosides are only approved for the treatment of manifest chronic heart failure (due to systolic dysfunction). Diuretics are indicated in the treatment of heart failure only when oedemas are due to heart failure or, as with the active ingredient hydrochlorothiazide, as adjunctive symptomatic therapy for chronic heart failure in addition to ACE inhibitors.

on 2. Non-medicinal treatment options are not considered in the present therapeutic indication as a rule.

on 3. The following resolutions of the G-BA are available:

Guideline of the G-BA on the combination of requirements for structured treatment programmes according to Section 137f paragraph 2 SGB V (DMP Requirements Guideline/DMP-A-RL)

- There are requirements for structured treatment programmes for patients with chronic heart failure (https://www.g-ba.de/downloads/62-492-2574/DMP-A-RL_2021-03-18_iK-2021-10-01.pdf).

Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V (Annex XII AM-RL)

- Sacubitril/valsartan (resolution of 16 June 2016)
- Dapagliflozin (resolution of 20 May 2021)
- Empagliflozin (resolution of 6 January 2022)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication.

According to the marketing authorisation, vericiguat is used in patients with symptomatic, chronic heart failure with reduced ejection fraction who are stabilised after a recent decompensation event. Taking into account thatthe patients are in a stable condition, the underlying disease of symptomatic, chronic heart failure with reduced ejection fraction is considered when determining the appropriate comparator therapy.

The present study assumes that vericiguat is used in addition to standard therapy for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

The guidelines recommend both ACE inhibitors and beta-adrenoceptor antagonists for patients with heart failure in all NYHA classes. AT1 receptor blockers (ARBs) are recommended for ACE inhibitor intolerance according to the marketing authorisation. Mineralocorticoid receptor antagonists (MRAs) are recommended in NYHA class II-IV patients who remain symptomatic despite therapy with an ACE inhibitor and beta-adrenoceptor antagonists. According to guidelines, the use of diuretics in patients with heart failure and reduced ejection fraction of NYHA classes II, III and IV - in addition to standard therapy - is only recommended if there are also signs of fluid retention.

According to guideline recommendations[2], therapy should be intensified if the symptomatology persists under a basic therapy. Accordingly, in patients who are symptomatic despite guideline-compliant therapy with an ACE inhibitor (or ARB), a beta-adrenoceptor antagonist and an MRA, intensification of medicinal therapy with an SGLT-2 inhibitor or with sacubitril/valsartan is recommended as the next step. In this case, treatment with an SGLT-2 inhibitor should be independent of diabetes status; the switch to sacubitril/valsartan is made in exchange for the ACE inhibitor/ARB.

In the early benefit assessment, sacubitril/valsartan and the SGLT-2 inhibitors dapagliflozin and empagliflozin were assessed in the present therapeutic indication. For the combination of active ingredients sacubitril/valsartan, a hint for a considerable (adults without diabetes mellitus) or for a minor (adults with diabetes mellitus) additional benefit was found. With regard to the SGLT-2 inhibitors, a hint for a considerable additional benefit was found for dapagliflozin and a hint for a minor additional benefit was found for empagliflozin. Against the background of the changes taking place in the medicinal treatment of heart failure and taking into account the guideline recommendations, sacubitril/valsartan, dapagliflozin and empagliflozin are to be regarded as the standard in heart failure therapy, provided that further intensification of medicinal therapy is indicated.

Due to their limited safety profile, digitalis glycosides are recommended mainly in the second-line setting only as an additional reserve agent if patients with reduced ejection

[2] https://www.leitlinien.de/nvl/html/nvl-chronische-herzinsuffizienz/3-auflage/kapitel-6#section-1

fraction and sinus rhythm remain symptomatic despite optimum therapy. This product class is therefore not regularly considered as an appropriate comparator therapy in the present therapeutic indication. The same is true for ivabradine, as it is only recommended in beta-adrenoceptor antagonists intolerance or only additively in patients with heart rates ≥ 75/min.

In light of the above, an optimised standard therapy for the treatment of symptomatic chronic heart failure and underlying conditions, such as hypertension, arrhythmias, coronary heart disease, diabetes mellitus, hypercholesterolaemia, and concomitant symptoms is determined to be an appropriate comparator therapy for vericiguat for the treatment of adults with symptomatic chronic heart failure with reduced ejection fraction.

Since the administration of vericiguat is in addition to standard therapy, it is assumed that the patients in both study arms will be treated optimally: a guideline-compliant patient-individual treatment of heart failure and underlying diseases or risk factors such as hypertonia, cardiac arrhythmias or diabetes mellitus as well as concomitant symptoms, such as oedema, is assumed. The adequate treatment of the underlying disease should be documented in the dossier on the basis of the patient characteristics (e.g. HbA1c value, oedema, cardiac arrhythmias, etc.). The marketing authorisations and product information of the medicinal products are to be observed; deviations are to be justified separately.

Adjustment of the basic/concomitant medication to the respective needs of the patient is to take place in both study arms. Therapy adjustment may include dosage adjustments as well as changes of therapy or therapy initiation for the treatment of new symptoms as well as for the deterioration of existing symptoms. The concomitant and basic medication at the start of study as well as changes regarding the concomitant or basic medication must be documented.

The additional benefit is determined compared to the appropriate comparator therapy. The unchanged continuation of an inadequate therapy does not correspond to the appropriate comparator therapy. If there is no further possibility of optimisation, it must be documented and explained that any other existing treatment options are not suitable or have been exhausted.

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

2.1.3 Extent and probability of the additional benefit

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

<u>Adults with symptomatic, chronic heart failure with reduced ejection fraction who are stabilised after a recent decompensation event requiring IV therapy</u>

Hint for a minor additional benefit

Justification:

For the assessment of the additional benefit of vericiguat, the pharmaceutical company presents the placebo-controlled, double-blind, randomised VICTORIA study, in which patients with chronic heart failure of NYHA classes II to IV and reduced left ventricular ejection fraction (LVEF) ≤ 45% were examined. In addition, participants had to have elevated NT-proBNP[3]levels and have suffered a decompensation event for enrolment in the study. Inclusion criteria were a decompensation event as hospitalisation due to heart failure within six months and/or treatment of heart failure with IV -diuretics (without hospitalisation) within the last three months prior to the start of treatment.

According to the study protocol, adequate medicinal therapy for heart failure should be given according to locally relevant guidelines, at the discretion of the principal investigator and patient-individual tolerance. The medicinal therapy of heart failure in the study consisted of combinations of the product classes ACE inhibitors, ARB[4], beta-adrenoceptor antagonists, oral diuretics, MRA[5] and the ARNI[6] sacubitril/valsartan. If necessary, the supply of implantable cardioverters or defibrillators (ICD) and biventricular pacemakers should also be ensured.

A total of 5,050 study participants were enrolled (of which 4,316 were in the relevant target population with reduced ejection fraction and LVEF < 40%) and randomised in a 1:1 ratio to the two study arms vericiguat versus placebo (2,158 participants per study arm in the relevant target population). Patient-relevant results were recorded in the categories of mortality, morbidity, health-related quality of life and side effects. The study was event-controlled, with a median treatment duration of about 1 year.

Uncertainty of the study population

According to the marketing authorisation, vericiguat is indicated for the treatment of adults with symptomatic chronic heart failure with reduced ejection fraction who are stabilised following a recent decompensation event requiring IV therapy. Although IV therapy was not an explicit inclusion criterion for study participants hospitalised for a decompensation event, it is assumed that IV treatment is usually given during hospitalisation for heart failure. However, the requirement that patients are stabilised after the decompensation event was only addressed by the fact that the IV therapy had to be longer ago than 24 hours. It is unclear whether a time span of 24 hours was sufficient in all cases to ensure stabilisation of the patients. Consequently, it is uncertain whether all the adults examined in the study were clinically stable without exception.

Implementation of the appropriate comparator therapy

In the VICTORIA study, all patients were to receive a patient-individual therapy according to locally valid, e.g. European guidelines. Adjustments to heart failure therapy were possible at any time before and during the study.

At the start of the study, a total of 73% of patients received treatment with ACE inhibitors or ARBs, about 93% received beta-blockers and 72% also received MRA. With regard to the therapy adjustments made during the study, 39% of study participants in the intervention arm

[3] NT-proBNP: N-terminal pro-B-type natriuretic peptide
[4] ARB: AT1 receptor blocker
[5] Mineralocorticoid receptor antagonist
[6] ARNI: Angiotensin receptor-neprilysin inhibitor

versus 41% in the comparison arm started a new medicinal therapy for the treatment of heart failure or increased the dose of the standard therapy, while 44% in each treatment arm changed their therapy by reducing the dose or discontinuing the standard therapy. The pharmaceutical company's dossier does not include detailed information on the product classes to which the study participants switched during the study. Detailed information on the type of therapy adjustments carried out as well as the therapies for the treatment of comorbidities and their adjustments are also not available.

Approximately 60% of the study participants in the comparator arm did not experience any therapy adjustment during the study. In view of the fact that there is a higher risk for the target population to suffer further decompensation events due to the inclusion criteria, it cannot be conclusively assessed whether it can be safely assumed that the percentage of patients without therapy adjustments in the control arm was already optimally treated at the start and in the further course of the study, or whether no further therapy optimisations were possible.

According to guideline recommendations[2] in the case of persisting symptomatology despite guideline-compliant therapy with an ACE inhibitor (or ARB), a beta-adrenoceptor antagonist and an MRA, intensification of therapy should be considered with sacubitril/valsartan or with the recently approved SGLT-2 inhibitors.

With regard to the use of sacubitril/valsartan, it is noted that 16% of patients were pretreated with sacubitril/valsartan at the start of the study; this percentage increased to 20% in the intervention arm and 21% in the comparator arm between weeks 17 and 32, and the percentages changed only slightly to 19% and 22%, respectively by late treatment between weeks 113 and 128. On the one hand, it is assumed that the escalation with sacubitril/valsartan in the study largely corresponds to the reality of care in Germany. On the other hand, the dossier shows that treatment with sacubitril/valsartan was not available for 19% of the participants in the study.

With regard to treatment with SGLT-2 inhibitors, which were not approved for the treatment of chronic heart failure but only for the treatment of type 2 diabetes mellitus at the time the study was conducted, 0.9% received dapagliflozin and 3.5% empagliflozin in the VICTORIA study, in each case only as part of diabetes therapy.

Overall, it is concluded that against the background of the current changes in the medicinal therapy of heart failure, the current reality of care and clinical practice in Germany do not fully correspond to the current guideline recommendations.

With regard to the treatment of the underlying diseases or risk factors, neither recommendations nor limitations were given in the VICTORIA study.

The dossier contains data on the mean change in HbA1c in diabetics and systolic blood pressure in hypertensive patients at different time points during the study. This shows that although the study participants had a mean HbA1c value and systolic blood pressure within the recommended target values, it is unclear whether or what therapy adjustments were made to treat the underlying diseases and risk factors. The pharmaceutical company does not provide information on the medicinal therapy carried out in the study, for example with diuretics or other medicinal products such as antithrombotics or lipid-lowering agents. A conclusive assessment of the medicinal therapy of the underlying diseases and risk factors is therefore not possible.

In the overall assessment, it cannot be clearly assessed whether all optimisation options as part of the appropriate comparator therapy, if further adjustment was indicated, were

actually exhausted within the framework of the patient-individual therapy carried out in the study. In particular, the appropriate comparator therapy was implemented in a limited way due to the fact that not all therapy options recommended in the guidelines, e.g. sacubitril/valsartan or SGLT-2 inhibitors, were available for all patients in the study. The VICTORIA study is used for the benefit assessment despite these remaining uncertainties regarding the implementation of the appropriate comparator therapy.

Extent and probability of the additional benefit

Mortality

Overall mortality and cardiovascular death presented additionally

There are no statistically significant differences between the treatment arms, neither for the endpoint "overall mortality" nor for the endpoint *"cardiovascular death"* presented additionally.

Morbidity

Total hospitalisation

The endpoint "total hospitalisation" was not planned in the VICTORIA study; no more precise information on the operationalisation is available. From the data submitted in the written statement procedure, there is a statistically significant advantage of vericiguat in terms of "total hospitalisation" compared to the control arm.

Hospitalisation due to heart failure

The endpoint *"hospitalisation due to heart failure"* is presented additionally in the present case. This results in a statistically significant difference to the advantage of vericiguat compared to the comparator arm. In addition, effect modification is observed with respect to age: for adults younger than 75 years, there were statistically significantly fewer hospitalisations due to heart failure in the vericiguat arm compared to control, and for adults aged 75 years or older, there were no statistically significant differences between the treatment arms.

Myocardial infarction and stroke

For the endpoints "myocardial infarction" and "stroke", there were no statistically significant differences between the treatment arms.

Health status

Health status was assessed in the study using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the improvement by ≥ 15 points at week 32, there is no statistically significant difference between the treatment arms.

Quality of life

Kansas City Cardiomyopathy Questionnaire (KCCQ)

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

The KCCQ is a disease-specific questionnaire to assess health-related quality of life in patients with cardiomyopathy, which is completed by the affected patients 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 (overall summary score) is used for the early benefit assessment.

According to IQWiG's current methodological approach (methods paper 6.1, published on 24.01.2022), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of exactly 15% of the scale range) to be necessary for patient-reported endpoints in order to represent a noticeable change with sufficient certainty.

For the clinical sum score KCCQ-OSS, operationalised as an improvement of ≥ 15%, there were no statistically significant differences between the treatment arms.

The pharmaceutical company submits evaluations of responder analyses using the criterion of improvement by ≥ 5 points compared to the baseline at week 32. This results in a statistically significant difference to the advantage of vericiguat compared to the comparator arm. These results are taken into account in the present case.

Side effects

In the side effects category, results are available for the overall rate of serious adverse events, discontinuation due to adverse events, and data on specific adverse events.

Overall rates

Serious adverse events (SAE)

For the endpoint of SAE, there are no statistically significant differences between the treatment groups.

Discontinuation due to adverse events (AEs)

For the endpoint of discontinuation due to AEs, there were no statistically significant differences between the treatment groups.

Specific AEs

Hypotension

In detail, there are no statistically significant differences between the treatment groups for the specific AE hypotension (PT[7], SAE).

Blood and lymphatic system disorders

In detail, for the endpoint of blood and lymphatic system disorders (SOC[8], SAE), there is a statistically significant difference between the treatment groups to the disadvantage of vericiguat compared to the comparator arm.

Atrial fibrillation

In detail, for the endpoint of atrial fibrillation (PT, SAE), there is a statistically significant difference between the treatment groups to the advantage of vericiguat over the comparator arm.

[7] PT: preferred term
[8] SOC: system organ class

Overall assessment / conclusion

For the early benefit assessment of vericiguat post market launch for the therapeutic indication of treatment of symptomatic chronic heart failure in adults with reduced ejection fraction stabilised after a recent decompensation event requiring IV therapy, the pharmaceutical company presents the placebo-controlled, double-blind, randomised VICTORIA study. Patients with chronic heart failure of NYHA classes II to IV with reduced LVEF, who also had elevated NT-proBNP values and had previously suffered a decompensation event, were studied. The median treatment duration was about 1 year.

For the mortality category, for the endpoint "overall mortality" and for the endpoint *"cardiovascular mortality",* presented additionally, there were no statistically significant differences between the treatment arms.

In the morbidity category, a statistically significant advantage of vericiguat over the comparator arm is observed for the endpoint "total hospitalisation".

Other endpoints in the morbidity category: Myocardial infarction, stroke and health status, assessed by the EQ-5D VAS, do not show statistically significant differences between the treatment arms.

In the category of health-related quality of life, data are available for the clinical sum score KCCQ-OSS in two operationalisations, which show different effects depending on the operationalisation. There are no statistically significant differences for the operationalisation as an improvement of ≥ 15%. For the improvement of ≥ 5 points, there is a statistically significant difference to the advantage of vericiguat.

In the category of side effects, no statistically significant differences are found between the groups for the overall rate of SAEs and discontinuation due to AEs.

For the specific AEs, there was a statistically significant difference in the endpoint of blood and lymphatic system disorders (SOC, SAE) to the disadvantage of vericiguat compared to the control, while for the endpoint of atrial fibrillation (PT, SAE), there was a statistically significant difference to the advantage of vericiguat. No statistically significant differences were found for the endpoint of hypotension.

In the overall assessment of the results based on the positive effects of vericiguat in avoiding total hospitalisations and improving the quality of life (operationalised as an improvement of ≥ 5 points in the KCCQ-OSS:), a minor additional benefit of vericiguat compared to the appropriate comparator therapy is determined.

Reliability of data (probability of additional benefit)

Overall, the study has uncertainties that limit the significance of the results.

The study medication, vericiguat or placebo, should be administered in addition to patient-individual heart failure therapy according to local guidelines. Adjustments to the heart failure therapy were possible at any time prior to the study and in the course thereof. With regard to the treatment of the underlying diseases or risk factors, neither recommendations nor limitations were given in the study.

An optimised standard therapy for the treatment of symptomatic, chronic heart failure and the underlying diseases was named as the appropriate comparator therapy. However, the current guideline recommendations were only implemented to a limited extent in the study against the backdrop of the current changes in medicinal therapy for heart failure. On the one hand, it is unclear whether all optimisation options have actually been exhausted. On the

other hand, not all medicinal products recommended by the guidelines (sacubitril/valsartan, SGLT-2 inhibitors) were available for all study participants.

Due to the uncertainties described above, the reliability of data is classified under the "hint" category.

2.1.4 Summary of the assessment

This is the early benefit assessment of the new active ingredient vericiguat (Verquvo®) approved for the treatment of adults with symptomatic, chronic heart failure with reduced ejection fraction who are stabilised after a recent decompensation event requiring IV therapy.

An optimised standard therapy for the treatment of symptomatic, chronic heart failure and the underlying diseases, such as hypertonia, cardiac arrhythmias, coronary heart disease, diabetes mellitus, hypercholesterolaemia, as well as the concomitant symptoms, was determined as the appropriate comparator therapy.

The VICTORIA study, which investigated the administration of vericiguat versus placebo, in each case in addition to standard heart failure therapy, in patients with NYHA classes II to IV chronic heart failure with reduced ejection fraction was presented. The patients had one decompensation event in the past.

In the mortality category, there were no statistically significant differences in the avoidance of deaths.

In the morbidity category, there is a statically significant advantage of vericiguat over the control arm for total hospitalisation. There were no statistically significant differences in the cardiovascular morbidity endpoints myocardial infarction and stroke.

In the category of health-related quality of life, there was an advantage of vericiguat for the clinical sum score KCCQ-OSS, operationalised as an improvement of ≥ 5 points. However, no statistically significant differences are found for the operationalisation as improvement by ≥ 15% of the KCCQ-OSS scale range.

In the category of side effects, there are no statistically significant differences between the treatment arms for the overall rate of SAEs and discontinuation due to AEs. For the specific AEs, there was a statistically significant difference in the endpoint of blood and lymphatic system disorders (SOC, SAE) to the disadvantage of vericiguat compared to the control, while for the endpoint of atrial fibrillation (PT, SAE), there is a statistically significant difference to the advantage of vericiguat.

Overall, the study is subject to uncertainties, especially in the implementation of the appropriate comparator therapy with regard to the exploitation of optimisation options and due to the fact that not all medicinal products recommended by the guidelines (sacubitril/valsartan, SGLT2 inhibitors) were available for all study participants.

In the overall assessment, a hint for a minor additional benefit is determined.

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.

Overall, the information provided by the pharmaceutical company is subject to uncertainties, but is taken into account here despite the uncertainties.

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 Verquvo (active ingredient: Vericiguat) at the following publicly accessible link (last access: 21. December 2021):

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 February 2022).

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 is patient-individual 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.

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. The recommended dose of vericiguat for maintenance treatment is 1 x daily 10 mg.

From the appropriate comparator therapy "An optimised standard therapy for the treatment of symptomatic, chronic heart failure and the underlying diseases, such as hypertonia, cardiac arrhythmias, coronary heart disease, diabetes mellitus, hypercholesterolaemia as well as the concomitant symptoms" includes many treatment options that differ greatly in their nature. Symptomatic chronic heart failure is treated particularly with angiotensin-converting enzyme (ACE) inhibitors, AT1 receptor blockers (ARBs), beta-adrenoceptor antagonists, mineralocorticoid receptor antagonists (MRAs), diuretics and SGLT-2 inhibitors.

Since the optimised standard therapy of heart failure is patient-individual, no specific costs for the appropriate comparator therapy can be mentioned here. In addition, optimised standard therapy for the treatment of symptomatic chronic heart failure and the underlying diseases is provided in the context of both the medicinal product empagliflozin to be assessed and the appropriate comparator therapy.

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				
Vericiguat	Continuously, 1 x daily	365	1	365
+ Optimised standard therapy	Different from patient to patient			
Appropriate comparator therapy				
+ Optimised standard therapy	Different from patient to patient			

Consumption:

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					
Vericiguat	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
+ Optimised standard therapy	Different from patient to patient				
Appropriate comparator therapy					
Optimised standard therapy	Different from patient to patient				

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.

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					
Vericiguat 10 mg	98 FCT	€ 438.74	€ 1.77	€ 23.67	€ 413.30
+ Optimised standard therapy	Different from patient to patient				
Appropriate comparator therapy					
Optimised standard therapy	Different from patient to patient				
Abbreviations: FCT = film-coated tablets					

LAUER-TAXE® last revised:15 February 2022

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.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 May 2021.

On 14 September 2021, the pharmaceutical company submitted a dossier for the benefit assessment of Vericiguat to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 15 September 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 Vericiguat.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 December 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 December 2021. The deadline for submitting written statements was 5 January 2022.

The oral hearing was held on 24 January 2022.

By letter dated 25 January 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 11 February 2022.

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 were discussed at the session of the subcommittee on 22 February 2022, and the draft resolution was approved.

At its session on 3 March 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	26 May 2020	Determination of the appropriate comparator therapy
Working group Section 35a	18 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	25 January 2022	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	01.02.2022; 15.02.2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	22 February 2022	Concluding discussion of the draft resolution
Plenum	3 March 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 March 2022

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

Prof. Hecken