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) and

Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Finerenone (new therapeutic indication: chronic kidney disease in type 2 diabetes, stages 1 and 2 with albuminuria)

of 17 August 2023

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 active ingredient finerenone (Kerendia) was listed for the first time on 1 October 2022 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 6 February 2023, Kerendia received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 22 February 2023, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of

Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1 number 2 Rules of Procedure of the G-BA (VerfO) on the active ingredient finerenone with the new therapeutic indication "Treatment of chronic kidney disease (stages 1 and 2 with albuminuria) associated with type 2 diabetes in adults".

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 June 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 finerenone 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 finerenone.

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 Finerenone (Kerendia) in accordance with the product information

Kerendia is indicated for the treatment of chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults.

Therapeutic indication of the resolution (resolution of 17.08.2023):

Kerendia is indicated for the treatment of chronic kidney disease (stages 1 and 2 with albuminuria) associated with type 2 diabetes in adults.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with chronic kidney disease (stages 1 and 2 with albuminuria) associated with type 2 diabetes

Appropriate comparator therapy:

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

An optimised standard therapy for the treatment of chronic kidney disease and type 2 diabetes mellitus, taking into account the underlying disease(s) and common comorbidities (such as dyslipoproteinaemia, hypertension, anaemia, heart failure)

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. 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.

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

on 1. Dapagliflozin is approved for the treatment of chronic kidney disease.

For the treatment of the underlying disease, type 2 diabetes mellitus, and frequent comorbidities such as hypertension, dyslipoproteinaemia, anaemia or secondary diseases, the medicinal products approved for the respective indications are used.

on 2. A non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication.

on 3. Resolution on the benefit assessment of dapagliflozin according to Section 35a SGB V of 17 February 2022.

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.

Overall, the evidence in the present therapeutic indication is limited. According to guideline recommendations, treatment of chronic kidney disease includes the use of ACE inhibitors or AT 1 antagonists if they are eligible and are not contraindicated or intolerable. According to the generally recognised state of medical knowledge and taking into account the opinion of the experts in the written statement procedure, the significance of dapagliflozin for the treatment of chronic kidney disease - across all stages - is also emphasised in the meantime.

For dapagliflozin, a hint for a considerable additional benefit was identified for adults with chronic kidney disease without symptomatic chronic heart failure as a comorbidity, and a hint for a minor additional benefit was identified for adults with chronic kidney disease with additional symptomatic chronic heart failure as a comorbidity.

Therefore, dapagliflozin is added to the selection of active ingredients to be used.

In addition, the therapeutic focus is on the treatment of the underlying disease, type 2 diabetes mellitus, and frequent comorbidities (e.g. hypertension, dyslipoproteinaemia, anaemia, heart failure, etc.). The marketing authorisation and dosage specifications in the product information of the active ingredients must be considered; deviations must be justified separately. Based on the aggregated evidence, a sufficiently safe recommendation for the use of SGLT2 inhibitors for the treatment of patients with CKD in combination with type 2 diabetes mellitus can also be made at this time. Based on the results of cardiovascular outcome studies and the recommendations of the guideline[2] , the most robust data have been shown in diabetics with existing cardiovascular disease and therefore the use of a GLP-1 agonist (liraglutide) and/or an SGLT2 inhibitor (empagliflozin, dapagliflozin) is considered part of the optimised standard therapy in patients with cardiovascular disease.

Accordingly, it is assumed that the optimised standard therapy for the treatment of chronic kidney disease and type 2 diabetes mellitus, taking into account the underlying disease(s) and frequent comorbidities (such as dyslipoproteinaemia, hypertension, anaemia, heart failure) or secondary diseases, also includes the use of SGLT2 inhibitors (specifically dapagliflozin) in addition to ACE inhibitors or AT-1 antagonists.

Placebo or the unchanged continuation of an inadequate therapy of the underlying disease does not correspond to the appropriate comparator therapy if there are other options for optimising the therapy.

For the target population to be treated, target values for comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) are to be defined prior to the start of the study, which the patients should reach before the start of the study or possibly during a run-in phase and maintain during the study by means of patient-individual therapy (e.g. dose adjustments). The target values should be based on the treatment standards of the corresponding diseases and, if necessary, take multiple comorbidities into account.

2 National Health Care Guideline Type 2 Diabetes, Version 3.0, 2023.

Overall, it is assumed that a slowing of disease progression in patients is continued to be sought in the planned therapeutic indication, so that renal replacement therapy in the form of dialysis or transplantation is not yet indicated.

Taking into account the treatment options as well as the recommendations, the G-BA determines an optimised standard therapy for the treatment of chronic kidney disease and type 2 diabetes mellitus as an appropriate comparator therapy, taking into account the underlying disease(s) and frequent comorbidities (such as dyslipoproteinaemia, hypertension, anaemia, heart failure) or secondary diseases.

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.

2.1.3 Extent and probability of the additional benefit

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

Adults with chronic kidney disease (stages 1 and 2 with albuminuria) associated with type 2 diabetes

Hint for a non-quantifiable additional benefit.

Justification:

The pharmaceutical company presents the FIDELIO-DKD and FIGARO-DKD studies for the assessment of the additional benefit of finerenone.

FIDELIO-DKD and FIGARO-DKD studies

The FIDELIO-DKD study is a placebo-controlled, double-blind, randomised, parallel-group study of finerenone conducted from September 2015 to April 2020. Patients with type 2 diabetes mellitus according to the American Diabetes Association and CKD with a urine albumin creatinine ratio (UACR) ≥ 30 to < 300 mg/g and an eGFR of ≥ 25 to < 60 ml/min/1.73 m^2 or a UACR of ≥ 300 mg/g and an eGFR of ≥ 25 to < 75 ml/min/1.73 m^2 were enrolled. A total of 5734 patients were enrolled and assigned in a 1:1 ratio to treatment with finerenone (N = 2866) or to the placebo group (N = 2868).

The primary endpoint of the study was the composite endpoint consisting of the components kidney failure, sustained decrease in eGFR by ≥ 40% and renal death. Patient-relevant endpoints were assessed in the categories of mortality, morbidity, health-related quality of life and side effects.

The FIGARO-DKD study is a placebo-controlled, double-blind, randomised, parallel-group study of finerenone conducted from September 2015 to February 2021. Patients with type 2 diabetes mellitus according to the American Diabetes Association and CKD with a UACR of ≥ 30 to < 300 mg/g and an eGFR of ≥ 25 to ≤ 90 ml/min/1.73m^2 or with a UACR of ≥ 300 mg/g and an eGFR of ≥ 60 ml/min/1.73m^{2}were enrolled. A total of 7437 patients were enrolled and assigned in a 1:1 ratio to treatment with finerenone (N = 3723) or to the placebo group (N = 3714). The primary endpoint of the study was the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for heart failure. Other patient-relevant endpoints were assessed in the categories of mortality, morbidity, health-related quality of life and side effects.

In both studies, patients had to be treated with a maximally tolerated and stable dose of ACE inhibitors or ARBs for at least 4 weeks before screening, which was ensured as part of therapy optimisation during the run-in phase. Patients with known non-diabetic kidney disease or symptomatic chronic heart failure of New York Heart Association (NYHA) class II to IV and with reduced left ventricular ejection fraction (HFrEF) were excluded. Patients with uncontrolled arterial hypertension of ≥ 160/100 mmHg at the time of screening or glycated haemoglobin (HbA1c) levels of > 12% were also excluded. Eplerenone, spironolactone, renin inhibitors and potassium-sparing diuretics were not allowed from 4 weeks before screening. According to the study protocol, the study participants of both studies should be treated with an individually adapted therapy according to local guidelines and recommendations for CKD, type 2 diabetes mellitus and any other comorbidities.

Relevant sub-populations of the FIDELIO-DKD and FIGARO-DKD studies

To answer the question, the diagnostic criteria of the Kidney Disease: Improving Global Outcomes (KDIGO) guideline, sub-populations of the FIDELIO-DKD and FIGARO-DKD studies were formed. The criterion used for stage 1 and 2 CKD is an eGFR ≥ 60 ml/min/1.73m^2 and a UACR ≥ 30 mg/g. As only patients with albuminuria (UACR ≥ 30 mg/g) were enrolled in both studies, the pharmaceutical company allocated the patients exclusively according to the criterion eGFR ≥ 60 ml/min/1.73m^2. The division by the pharmaceutical company results in a sub-population of 432 patients (211 in the intervention arm and 221 in the comparator arm) from the FIDELIO-DKD study and a sub-population of 4,631 patients (2,327 in the intervention arm and 2,304 in the comparator arm) from the FIGARO-DKD study.

Suitability of the study for the benefit assessment: Implementation of the appropriate comparator therapy

The comparison submitted by the pharmaceutical company is subject to uncertainties with regard to the implementation of the appropriate comparator therapy. Despite these uncertainties, a sufficient approximation to the appropriate comparator therapy is assumed overall, so that the present studies can be used for the benefit assessment.

It cannot be conclusively assessed to what extent the standard therapy carried out in the study corresponds to a treatment of chronic kidney disease associated with diabetes mellitus recommended according to the current state of medical knowledge.

Since 2022, the KDIGO guideline for the treatment of diabetes mellitus in chronic kidney disease recommends treatment with an SGLT2 inhibitor for patients with type 2 diabetes, chronic kidney disease and a GFR of 20 ml/min per 1.73m^2 or more.[3]

The German NVL type 2 Diabetes recommends the use of SGLT2 inhibitors or GLP-1 receptor agonists (GLP-1-RA), especially in patients with high cardiovascular risk or manifest cardiovascular disease.[4] In the relevant sub-population, about 35% of the patients had a previous cardiovascular disease at the start of the study.

In addition, the G - BA determined a considerable additional benefit of dapagliflozin for patients with CKD without symptomatic, chronic heart failure as a comorbidity in its resolution of 17 February 2022.

Given the current evidence, comprehensive transferability to the current healthcare context would have required a correspondingly extensive use of SGLT2 inhibitors - particularly dapagliflozin for the treatment of CKD - within the studies. However, in the FIGARO-DKD and FIDELIO-DKD studies, patient-individual antidiabetic therapy was possible, with no restrictions on the choice of medicinal therapies. Treatment with SGLT2 inhibitors/ GLP-1-RA was allowed within the study and the percentage of patients in the comparator arm receiving an SGLT2 inhibitor/ GLP-1-RA was 16-17% in each of the FIDELIO-DKD and FIGARO-DKD studies, newly initiated antidiabetic therapy with SGLT2 inhibitors/ GLP-1-RA was included in 22.6% of patients in the FIDELIO-DKD study and 28.9% in the FIGARO-DKD study.

Overall, about 60% of the study participants started a new antidiabetic therapy in the course of the studies, so that it can be assumed that a patient-individual review and adjustment of the antidiabetic therapy took place. However, the mean HbA1c value, which was 7.8 per cent at the start of the start of the study, remained constant over the course of the study.

It can therefore be assumed that the antidiabetic therapy was applied equally in both arms and did not lead to any significant biases. The possibility of evaluating the efficacy endpoints is therefore considered to be given, with a reduction in significance overall.

In addition, the systolic blood pressure in both studies in the control and intervention arms, with an average value of 136 - 139 mmHg at the start of the study, was not in the target range for patients with CKD according to the current KDIGO guideline. Even though the target value of the study was not reached, the values are overall within the target range of the authoritative NVL recommendation (< 140 mmHg). In the course of the study, there was no relevant improvement in blood pressure values.

Against this background, there are doubts about the extent to which the standard therapy for the treatment of chronic kidney disease in type 2 diabetes (stages 1 and 2) carried out in the study corresponds to the current therapy standard. After careful consideration of the implementation of the appropriate comparator therapy, which is fraught with uncertainties, and the resulting limitation of the significance, the study results can be used for the benefit assessment. However, the uncertainties mentioned become apparent in the reliability of data.

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3 Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022 Nov;102(5S):S1-S127. doi: 10.1016/j.kint.2022.06.008.

4 National Health Care Guideline Type 2 Diabetes, Version 3.0, 2023.

Extent and probability of the additional benefit

Mortality

Overall mortality
For the endpoint of overall mortality, the meta-analysis of the FIDELIO-DKD and FIGARO-DKD studies showed a statistically significant advantage of finerenone over placebo.

Morbidity
Composite endpoint on renal morbidity
The composite endpoint of the renal morbidity studies includes the individual components kidney failure, eGFR decline ≥ 57% and renal death. Due to the high mean baseline eGFR values (approx. 80 ml/min/1.73m^2) of the patients, a sufficient patient relevance of the component eGFR decrease ≥ 57% cannot be assumed in the present situation. The composite endpoint is presented additionally.

Kidney failure
The composite endpoint of kidney failure consists of the components ESRD (end-stage renal disease, defined as the need for chronic dialysis treatment > 30 days, unless it is apparent that dialysis treatment can be stopped after 90 days, or renal transplantation) and a sustained decline in eGFR to < 15 ml/min/1.73 m². An ESRD is defined differently in the present therapeutic indication than for the therapeutic indication CKD 3/4, which is also to be assessed.
For the endpoint of kidney failure, the meta-analysis of the FIDELIO-DKD and FIGARO-DKD studies showed a statistically significant advantage of finerenone over placebo.

Confirmed deterioration of CKD to stage 4 or 5
Confirmed deterioration of CKD to stage 4 or 5 is patient-relevant. For the endpoint of confirmed deterioration of CKD to stage 4 or 5, the meta-analysis of the FIDELIO-DKD and FIGARO-DKD studies showed a statistically significant advantage of finerenone over placebo.

Cardiovascular morbidity (composite endpoint) and major cardiovascular events (operationalised as cardiovascular hospitalisation)
The composite endpoint of the cardiovascular morbidity studies includes the individual components of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and severe heart failure events (operationalised as hospitalisation due to heart failure). However, hospitalisations due to other cardiovascular reasons (e.g. hospitalisation due to atrial fibrillation, unstable angina pectoris or arrhythmias), which occurred more than twice as often as hospitalisations due to heart failure in the FIGARO-DKD study, are not included in the evaluations. The composite endpoint on cardiovascular morbidity thus covers only part of the relevant cardiovascular events.
The pharmaceutical company submitted evaluations for cardiovascular hospitalisation with its statement, which are, however, incomplete. Overall, the results of the composite endpoint are presented additionally.

Total hospitalisation

For the endpoint of total hospitalisation, there is no statistically significant difference between the treatment groups in the meta-analysis of the FIDELIO-DKD and FIGARO-DKD studies.

Health status (EQ-5D VAS) evaluated using MMRM

For the endpoint of health status collected by EQ-5D VAS, the meta-analysis of the FIDELIO-DKD and FIGARO-DKD studies do not show any statistically significant difference between the treatment groups.

Quality of life

KDQOL-36 evaluated using MMRM

PCS, MCS, kidney disease burden, symptoms and problems of kidney disease and impact of kidney disease on daily life

For the 5 domains of the KDQOL-36, PCS, MCS, kidney disease burden, symptoms and problems of kidney disease and impact of kidney disease on daily life of the KDQOL-36, the meta-analysis of the FIDELIO-DKD and FIGARO-DKD studies shows no statistically significant difference between the treatment groups in each case.

Side effects

AEs were recorded in the FIDELIO-DKD and FIGARO-DKD studies over the entire duration of observation, regardless of whether the patients were still receiving treatment with the study medication. In the evaluations presented on AEs, SAEs and AEs that lead to discontinuation, however, only events that occurred during treatment with the study medication and up to 3 days after therapy interruption or discontinuation are included. In the total population of the FIDELIO-DKD study, 53.6% in the intervention arm and 45.0% in the comparator arm interrupted therapy; in the total population of the FIGARO-DKD study, 50.3% in the intervention arm and 47.4% in the comparator arm interrupted therapy. This percentage is not expected to differ in the sub-population relevant for the benefit assessment. AEs that occurred during a therapy interruption of more than 3 days are therefore not included in the evaluation for a relevant percentage of patients. Similarly, patients who discontinued therapy with the study medication (22-24% in the FIDELIO-DKD study and 24-26% in the FIGARO-DKD study) are not included in the evaluations with their entire duration of observation.

For the endpoints of the side effects category, no suitable data are thus available.

Overall assessment

The placebo-controlled, double-blind, randomised FIDEO-DKD and FIGARO-DKD studies are available for the benefit assessment. They investigate the efficacy and safety of finerenone compared to placebo, in each case in addition to standard therapy, in patients with type 2 diabetes and chronic kidney disease (CKD) with albuminuria. The relevant sub-population is the patients in both studies with CKD 1+2.
In the mortality category, the endpoint "overall mortality" shows a statistically significant advantage of finerenone compared to the control arm.
In the morbidity category, the endpoints "kidney failure" and "confirmed deterioration of CKD to stage 4 or 5" each show a statistically significant advantage in favour of finerenone. For the other endpoints in the category of morbidity, health status and total hospitalisation, there are no statistically significant differences between the treatment arms.
In the health-related quality of life category, for the endpoint "KDQOL-36", there are likewise no statistically significant differences between treatment arms.
For the endpoints of the category side effects, no suitable data are available.
The overall assessment of the results shows positive effects on overall mortality and on the endpoints "kidney failure" and "confirmed deterioration of CKD to stage 4 or 5". However, due to the non-assessable results on adverse events, the weighing of the advantages shown in the study against harm aspects cannot be conclusively made, so that the extent of the additional benefit for adults with chronic kidney disease (stages 1 and 2 with albuminuria) associated with type 2 diabetes cannot be quantified.

Reliability of data (probability of additional benefit)

Overall, the FIDELIO-DKD and FIGARO-DKD studies show uncertainties that limit the significance of the results. Particularly with regard to the implementation of the appropriate comparator therapy with regard to the use of SGLT-2 inhibitors, there are uncertainties about the extent to which the study results can be transferred to the current German healthcare context. These have already been presented in detail under "Implementation of the targeted comparator therapy".
Furthermore, there is uncertainty that patients with symptomatic chronic heart failure with reduced left ventricular ejection fraction (HFrEF; NYHA stages II-IV) were not studied, although they are included in the therapeutic indication and represent a relevant patient group due to the associated very high risk of cardiovascular events and the associated increased mortality.
Against the background of these uncertainties, the reliability of data is therefore classified as "hint".

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient finerenone. The therapeutic indication assessed here is "Kerendia is indicated for the treatment of chronic kidney disease (stages 1 and 2 with albuminuria) associated with type 2 diabetes in adults".

The G-BA determined "an optimised standard therapy for the treatment of chronic kidney disease and type 2 diabetes mellitus, taking into account the underlying disease(s) and frequent comorbidities (such as dyslipoproteinaemia, hypertension, anaemia, heart failure)" as the appropriate comparator therapy.

The pharmaceutical company submits the relevant sub-populations of the FIDELIO-DKD and FIGARO-DKD studies, which investigate the efficacy and safety of finerenone compared to placebo, in each case in addition to standard therapy, in patients with type 2 diabetes and chronic kidney disease (CKD) with albuminuria.

For overall mortality, there is a statistically significant advantage of finerenone.

With regard to morbidity, the endpoints "kidney failure" and "confirmed deterioration of CKD to stage 4 or 5" show statistically significant advantages in favour of finerenone.

For health-related quality of life, there are no relevant differences between the treatment groups for the benefit assessment.

No suitable data are available for side effects category.

Overall, the study has uncertainties, particularly regarding the implementation of the appropriate comparator therapy and the exclusion of patients with symptomatic chronic heart failure with reduced left ventricular ejection fraction (HFrEF; NYHA stages II-IV).

In the overall assessment of the positive effects and the non-assessable results on adverse events, taking into account the uncertainties mentioned, the G-BA finds a hint for a non-quantifiable additional benefit.

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 G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, fraught with uncertainties. Uncertainties include, in particular, a possibly different prevalence in the meantime compared to the prevalence used in 2018, the potential enrolment of patients with chronic kidney disease not related to type 2 diabetes mellitus and the potential enrolment of patients without albuminuria.

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 Kerendia (active ingredient: finerenone) at the following publicly accessible link (last access: 27 April 2023):

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

No patients with symptomatic chronic heart failure with reduced left ventricular ejection fraction (HFrEF; NYHA stages II to IV) were studied.

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: 1 July 2023).

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.

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.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

According to the product information, serum potassium and eGFR must be measured again 4 weeks after the start or resumption of finerenone treatment or a dose increase of finerenone. Thereafter, serum potassium must be remeasured at regular intervals and as needed, based

on patient characteristics and serum potassium level. The maintenance dose (20 mg or 10 mg) depends on the measured serum potassium and eGFR values.

The appropriate comparator therapy "An optimised standard therapy for the treatment of chronic kidney disease and type 2 diabetes mellitus, taking into account the underlying disease(s) and common comorbidities (such as dyslipoproteinaemia, hypertension, anaemia)" includes many treatment options that are very different in nature. Chronic kidney disease is treated in particular with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (sartans).

Since the optimised standard therapy of chronic kidney disease is patient-individual, no specific costs for the appropriate comparator therapy can be mentioned here. In addition, the optimisation for the treatment of chronic stage 1 and 2 kidney disease with albuminuria and any comorbidities such as the type 2 diabetes present here is carried out both within the scope of the medicinal product finerenone to be assessed and within the scope of 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				
Finerenone	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					
Finerenone	10 mg or 20 mg	10 mg or 20 mg	1 x 10 mg or 20 mg	365	365 x 10 mg or 20 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					
Finerenone 10 mg	98 FCT	€ 355.73	€ 2.00	€ 32.69	€ 321.04
Finerenone 20 mg	98 FCT	€ 355.73	€ 2.00	€ 32.69	€ 321.04
+ 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: 1 July 2023

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.

2.5 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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designated medicinal products are each an active ingredient that can be used in combination therapy with the assessed medicinal product on the basis of an open-label combination. This results from the fact that, on the one hand, the product information for the assessed medicinal product does not contain any information on combination therapies and, on the other, this product information does not contain any information that regularly contradicts a combination therapy with the assessed medicinal product.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the specifications in the product information for the designated medicinal products, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive, which serves search purposes.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 23 March 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 22 February 2023, the pharmaceutical company submitted a dossier for the benefit assessment of finerenone to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 27 February 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 finerenone.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 May 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 June 2023. The deadline for submitting written statements was 22 June 2023.

The oral hearing was held on 10 July 2023.

By letter dated 11 July 2023, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 28 July 2023.

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 8 August 2023, and the proposed resolution was approved.

At its session on 17 August 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 March 2021	Determination of the appropriate comparator therapy
Working group Section 35a	4 July 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 July 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 July 2023 1 August 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	8 August 2023	Concluding discussion of the draft resolution
Plenum	17 August 2023	Resolution on the amendment of Annex XII and the amendment of Annex XIIa Pharmaceuticals Directive

Berlin, 17 August 2023

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

Prof. Hecken