Empagliflozin (renal insufficiency)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A23-78 Version: 1.0 Status: 30 October 2023

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Empagliflozin (Niereninsuffizienz) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Empagliflozin (renal insufficiency) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

31 July 2023

Internal Project No.

A23-78

Address of publisher

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Keywords

Empagliflozin, Renal Insufficiency – Chronic, Benefit Assessment

Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACE	angiotensin-converting enzyme
ACT	appropriate comparator therapy
AT-1	angiotensin-1
BSG	Bundessozialgericht (Federal Social Court)
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KDIGO	Kidney Disease Improving Global Outcomes
RAAS	renin-angiotensin-aldosterone system
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SGLT2	sodium-dependent glucose transporter-2
UACR	urinary albumin creatinine quotient

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug empagliflozin. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the “company”). The dossier was sent to IQWiG on 31 July 2023.

Research question

The research question presented in Table 2 is derived from the appropriate comparator therapy (ACT) specified by the G-BA.

Table 2: Research question of the benefit assessment of empagliflozin

Therapeutic indication	**ACT**[a]
Adults with CKD	Optimized standard therapy for CKD, taking into account the underlying illness and common comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia)[b]

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- The present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with § 35a (7), sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of CKD. According to the BSG comments on the judgement dated 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of § 2 (1), sentence 3, § 12 SGB V.
- According to current medical knowledge, the treatment of CKD presumably involves not only the use of ACE inhibitors or AT-1 antagonists, but also the use of SGLT2 inhibitors (in particular dapagliflozin), provided that they are therapeutically indicated for concomitant diseases or the underlying disease as per their marketing authorizations. The addition of SGLT2 inhibitors (in particular dapagliflozin) results from the change in the ACT in the decisions of the G-BA on finerenone dated 17 August 2023.
- Within the framework of the ACT, it is assumed that patients in both treatment arms receive individualized treatment of the underlying disease and any comorbidities in accordance with the current state of medical knowledge and avoiding the use of nephrotoxic drugs. The approval and dosing information of the drugs' SPCs must be adhered to, and any deviations justified separately.
- Placebo or the unchanged continuation of an inadequate treatment of the underlying disease does not correspond to an ACT if there are still further options for treatment optimization.
- For the target population to be treated, target values for comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) are to be defined before the start of the study; participants should reach these target values before the start of the study or, if applicable, during a run-in phase and maintain them during the study by means of individualized treatment (e.g. dose adjustments). The target values should be based on the treatment standards of the corresponding diseases and, if applicable, take multiple comorbidities into account.
- It is assumed that the treatment goal for the patients in the planned therapeutic indication remains to be a slowdown of disease progression, i.e. renal replacement therapy in the form of dialysis or transplantation is not yet indicated for the patients.

ACE: angiotensin-converting enzyme; ACT: appropriate comparator therapy; AkdÄ: Drug Commission of the German Medical Association; AT-1: angiotensin-1; BSG: Federal Social Court; CKD: chronic kidney disease; G-BA: Joint Federal Committee; SGB: German Social Code; SGLT2: sodium-dependent glucose transporter-2; SPC: Summary of Product Characteristics

In connection with the specification of the ACT, the G-BA has pointed out that the available guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with §35 a (7) sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of chronic kidney disease (CKD). According to the Federal Social Court (BSG) comments on the judgement dated 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the

Pharmaceuticals Directive are generally not considered as ACTs in the narrower sense of § 2 (1), sentence 3, § 12 SGB V.

Based on the ACT defined in the supporting reasons for the decisions of the G-BA on finerenone (in the therapeutic indication of adults with CKD in combination with type 2 diabetes), this benefit assessment adds sodium/glucose cotransporter 2 (SGLT2) inhibitors (specifically dapagliflozin) as an ACT alongside the ACTs mentioned in the G-BA's comment stating that, according to current medical knowledge, the treatment of CKD comprises the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-1 (AT-1) antagonists. In the supporting reasons, this addition of SGLT2 inhibitors, in particular dapagliflozin, to the ACT is justified by the fact that, according to generally recognized medical knowledge and taking into account the experts in the commenting procedure, there is now an emphasis on the importance of dapagliflozin in the treatment of CKD – across all stages. For dapagliflozin, a hint of considerable added benefit has been identified for adults with CKD without the comorbidity of symptomatic chronic heart failure, while a hint of a minor added benefit has been identified for adults with CKD with the additional comorbidity of symptomatic chronic heart failure. The G-BA therefore added dapagliflozin to the selection of drugs to be used. As the decisions on finerenone were taken in a therapeutic indication analogous to empagliflozin, it is presumed that the ACT currently determined for that indication also applies to the present benefit assessment.

The company followed the G-BA's specification of the ACT. However, the ACT did not yet include SGLT2 inhibitors (in particular dapagliflozin).

The present assessment is based on the ACT specified by the G-BA (see Table 2), which was adapted in accordance with the supporting reasons for the G-BA decisions on finerenone. The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for deriving any added benefit.

In the following, the term chronic renal insufficiency is used synonymously with the internationally more common term CKD, which is also used in the English-language SPC.

Results

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of empagliflozin in comparison with the ACT for the present research question.

The EMPA-KIDNEY study included by the company and the supplementary data presented by the company on subpopulations of the EMPA-REG OUTCOME, EMPEROR-Reduced, and

EMPEROR-Preserved studies are unsuitable for assessing the added benefit of empagliflozin compared with the ACT because they did not implement the ACT. This is justified below.

Evidence provided by the company

EMPA-KIDNEY study

The EMPA-KIDNEY study is a placebo-controlled, double-blind RCT on empagliflozin. It enrolled patients with CKD who exhibit a risk of disease progression and an estimated glomerular filtration rate (eGFR) of ≥ 20 to < 45 mL/min/1.73 m^2 or an eGFR of ≥ 45 to < 90 mL/min/1.73 m^2 with a urinary albumin creatinine quotient (UACR) of ≥ 200 mg/g (or a protein creatinine quotient of ≥ 300 mg/g). Patients were to receive an appropriate dose of renin-angiotensin-aldosterone system (RAAS) inhibitors (either ACE inhibitors or AT-1 antagonists) unless they did not tolerate such treatment or were not indicated for it. A total of 6609 patients were included and randomly assigned in a 1:1 ratio to treatment with empagliflozin (N = 3304) or to the placebo group (N = 3305). In addition, patients in both study arms were to receive individualized standard treatment from their treating physician, taking into account cardiovascular risk factors and existing comorbidities (e.g. high blood pressure, diabetes) and in accordance with local, national, or international guidelines.

The primary outcome of the study was a composite outcome of progression of kidney disease and cardiovascular mortality. Patient-relevant outcomes were recorded in the categories of mortality, morbidity, and side effects.

EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved studies

The 3 studies EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved are placebo-controlled RCTs on empagliflozin which have already been presented by the company in other benefit assessment procedures: the EMPA-REG OUTCOME study in the therapeutic indication of diabetes mellitus type 2, the EMPEROR-Reduced study in the therapeutic indication of symptomatic chronic heart failure with reduced ejection fraction, and the EMPEROR-Preserved study in the therapeutic indication of symptomatic chronic heart failure with preserved ejection fraction. The respective information on study design and characteristics of the corresponding overall study populations are presented in detail for the study EMPA-REG OUTCOME in dossier assessment A16-12, for the study EMPEROR-Reduced in dossier assessment A21-93, and for the study EMPEROR-Preserved in dossier assessment A22-39.

For reasons of completeness and transparency, the company reports having formed subpopulations from the 3 studies mentioned above based on the diagnostic criteria of the Kidney Disease Improving Global Outcomes (KDIGO) guideline and having presented the results as supplementary information. The criterion used was an eGFR < 60 mL/min/1.73 m^2 and/or a UACR ≥ 30 mg/g. It is unclear whether these criteria had already been met for at least

3 months by all these patients (as required by the KDIGO for the diagnosis of CKD). The company's classification results in a subpopulation with 2359 patients (1171 in the intervention arm and 1188 in the comparator arm) from the EMPA-REG OUTCOME study and a subpopulation of 6610 patients (3331 in the intervention arm and 3279 in the comparator arm) from the EMPEROR-Reduced and EMPEROR-Preserved studies which were combined by the company in the form of a metaanalysis.

ACT specified by the G-BA not implemented

As the ACT in the present therapeutic indication, the G-BA has specified optimized standard therapy for CKD treatment, taking into account the underlying disease and common comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia). According to current medical knowledge, the treatment of CKD is assumed to include not only ACE inhibitors or AT-1 antagonists, but also SGLT2 inhibitors (in particular dapagliflozin), provided that they are therapeutically indicated for concomitant diseases or the underlying disease in accordance with the marketing authorization. However, the EMPA-KIDNEY study and the 3 supplementary studies submitted by the company did not allow the use of SGLT2 inhibitors in principle, except as study medication in the intervention arm. In all 4 studies, the prohibition of SGLT2 inhibitors (except in the studies' intervention arms) prevented the treatment of CKD taking into account the underlying disease and common comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) as in the optimized standard therapy required per ACT. The EMPA-KIDNEY study submitted by the company and the supplementary data presented by the company on subpopulations of the EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved studies are therefore unsuitable for assessing added benefit in the present research question because the ACT has not been implemented.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of empagliflozin in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of the probability and extent of added benefit of empagliflozin.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Empagliflozin – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with CKD	Optimized standard therapy for CKD, taking into account the underlying illness and common comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia)[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- The present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with § 35a (7), sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of CKD. According to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of § 2 (1), sentence 3, § 12 SGB V.
- According to current medical knowledge, the treatment of CKD presumably involves not only the use of ACE inhibitors or AT-1 antagonists, but also the use of SGLT2 inhibitors (in particular dapagliflozin), provided that they are therapeutically indicated for concomitant diseases or the underlying disease as per their marketing authorizations. The addition of SGLT2 inhibitors (in particular dapagliflozin) is based on the change in the ACT in the G-BA decisions on finerenone dated 17 August 2023.
- Within the framework of the ACT, it is assumed that patients in both treatment arms receive individualized treatment of the underlying disease and any comorbidities in accordance with the current state of medical knowledge and avoiding the use of nephrotoxic drugs. The approval and dosing information of the drugs' SPCs must be adhered to, and any deviations justified separately.
- Placebo or the unchanged continuation of an inadequate treatment of the underlying disease does not correspond to an ACT if there are still further options for treatment optimization.
- For the target population to be treated, target values for comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) are to be defined before the start of the study; participants should reach these target values before the start of the study or, if applicable, during a run-in phase and maintain them during the study by means of individualized treatment (e.g. dose adjustments). The target values should be based on the treatment standards of the corresponding diseases and, if applicable, take multiple comorbidities into account.
- It is assumed that the treatment goal for the patients in the planned therapeutic indication remains to be a slowdown of disease progression, i.e. renal replacement therapy in the form of dialysis or transplantation is not yet indicated for the patients.

ACE: angiotensin-converting enzyme; AkdÄ: Drug Commission of the German Medical Association; AT-1: angiotensin-1; BSG: Federal Social Court; G-BA: Joint Federal Committee; CKD: chronic kidney disease; SGB: German Social Code; SGLT2: sodium-dependent glucose transporter-2; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of empagliflozin in comparison with optimized standard therapy as the ACT in patients with chronic kidney disease.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of empagliflozin

Therapeutic indication	**ACT**[a]
Adults with CKD	Optimized standard therapy for CKD, taking into account the underlying illness and common comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia)[b]

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- The present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with § 35a (7), sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of CKD. According to the BSG comments on the judgement of 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of § 2 (1), sentence 3, § 12 SGB V.
- According to current medical knowledge, the treatment of CKD presumably involves not only the use of ACE inhibitors or AT-1 antagonists, but also the use of SGLT2 inhibitors (in particular dapagliflozin), provided that they are therapeutically indicated for concomitant diseases or the underlying disease as per their marketing authorizations. The addition of SGLT2 inhibitors (in particular dapagliflozin) is based on the change in the ACT in the G-BA decisions on finerenone dated 17 August 2023.
- Within the framework of the ACT, it is assumed that patients in both treatment arms receive individualized treatment of the underlying disease and any comorbidities in accordance with current medical knowledge and avoiding the use of nephrotoxic drugs. The approval and dosing information of the drugs' SPCs must be adhered to, and any deviations justified separately.
- Placebo or the unchanged continuation of an inadequate treatment of the underlying disease does not correspond to an ACT if there are still further options for treatment optimization.
- For the target population to be treated, target values for comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) are to be defined before the start of the study; participants should reach these target values before the start of the study or, if applicable, during a run-in phase and maintain them during the study by means of individualized treatment (e.g. dose adjustments). The target values should be based on the treatment standards of the corresponding diseases and, if applicable, take multiple comorbidities into account.
- It is assumed that the treatment goal for the patients in the planned therapeutic indication remains to be a slowdown of disease progression, i.e. renal replacement therapy in the form of dialysis or transplantation is not yet indicated for the patients.

ACE: angiotensin-converting enzyme; ACT: appropriate comparator therapy; AkdÄ: Drug Commission of the German Medical Association; AT-1: angiotensin-1; BSG: Federal Social Court; CKD: chronic kidney disease; G-BA: Joint Federal Committee; SGB: German Social Code; SGLT2: sodium-dependent glucose transporter-2

In connection with the specification of the ACT, the G-BA pointed out that the available guidelines and scientific-medical societies and/or the Drug Commission of the German

Medical Association in accordance with § 35a (7) sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of CKD. According to the BSG comments on the judgement dated 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACTs in the narrower sense of § 2 (1), sentence 3, § 12 SGB V.

The G-BA has commented that, as per current medical knowledge, the treatment of CKD comprises the use of ACE inhibitors or AT-1 antagonists. In the present benefit assessment, SGLT2 inhibitors (specifically dapagliflozin) are added to these drugs based on the ACT defined in the supporting reasons for the G-BA decisions on finerenone (in the therapeutic indication of adults with CKD in combination with type 2 diabetes) [3,4]. The supporting reasons justify this addition of SGLT2 inhibitors, in particular dapagliflozin, to the ACT by arguing that, according to generally recognized medical knowledge and the experts involved in the commenting procedure, there is now an emphasis on the importance of dapagliflozin in the treatment of CKD – across all stages [3,4]. For dapagliflozin, a hint of considerable added benefit has been identified for adults with CKD without the comorbidity of symptomatic chronic heart failure, while a hint of a minor added benefit has been identified for adults with CKD with the additional comorbidity of symptomatic chronic heart failure. The G-BA therefore added dapagliflozin to the selection of drugs to be used. As the decisions on finerenone were taken in a therapeutic indication analogous to empagliflozin, it is presumed that the ACT currently determined for that indication also applies to the present benefit assessment.

The company followed the G-BA's specification of the ACT. However, the ACT did not yet include SGLT2 inhibitors (in particular dapagliflozin).

The present assessment is based on the ACT specified by the G-BA (see Section I 2), which was adapted in accordance with the supporting reasons for the G-BA decisions on finerenone [3,4]. The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for deriving any added benefit. This concurs with the company’s inclusion criteria.

In the following, the term chronic renal insufficiency is used synonymously with the internationally more common term CKD, which is also used in the English-language SPC.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on empagliflozin (status: June 2023)
- bibliographical literature search on empagliflozin (last search on 26 June 2023)
- search in trial registries / trial results databases for studies on empagliflozin (last search on 28 June 2023)
- search on the G-BA website for empagliflozin (last search on 28 June 2023)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 17 August 2023); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of empagliflozin in comparison with the ACT for the present research question. This deviates from the assessment of the company, which identified the RCT EMPA-KIDNEY [5] in its information retrieval and assessed added benefit mainly based on this study. In addition, the company presents supplementary data on subpopulations of the 3 studies EMPA-REG OUTCOME [6], EMPEROR-Reduced [7], and EMPEROR-Preserved [8] – for the 2 EMPEROR studies as a metaanalysis based on individual patient data (IPD).

The EMPA-KIDNEY study included by the company and the supplementary data presented by the company on subpopulations of the EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved studies are unsuitable for assessing the added benefit of empagliflozin compared with the ACT because they did not implement the ACT. This is justified below. The studies are described first. Thereafter, the reasons why the studies are not suitable for assessing the added benefit of empagliflozin compared to the ACT will be explained.

Evidence provided by the company

EMPA-KIDNEY study

The EMPA-KIDNEY study is a placebo-controlled, double-blind RCT on empagliflozin. It enrolled patients with CKD who exhibit a risk of disease progression and an eGFR of ≥ 20 to < 45 mL/min/1.73 m^2 or an eGFR of ≥ 45 to < 90 mL/min/1.73 m^2 with a UACR of ≥ 200 mg/g (or a protein creatinine quotient of ≥ 300 mg/g). According to the inclusion criteria, patients should be confirmed by the investigator to neither require empagliflozin (or another SGLT2 or SGLT1/2 inhibitor) nor be ineligible for such treatment. Furthermore, patients were to receive an appropriate dose of RAAS inhibitors (either ACE inhibitors or AT-1 antagonists) unless they

did not tolerate such treatment or it was not indicated. The study excluded patients with polycystic kidney disease, type 2 diabetes mellitus, and previous atherosclerotic cardiovascular disease with an eGFR > 60 mL/min/1.73 m^2 at screening as well as those taking SGLT2 or SGLT1/2 inhibitors or a combination of ACE inhibitors and AT-1 antagonists.

A total of 6609 patients were included and randomly assigned in a 1:1 ratio to treatment with empagliflozin (N = 3304) or to the placebo group (N = 3305). Stratification was based on age (< 45 years versus ≥ 45 to < 55 years versus ≥ 55 to < 65 years versus ≥ 65 to < 75 years versus ≥ 75 years), sex (male versus female), existing diabetes (yes versus no), eGFR at the time of screening (< 30 mL/min/1.73 m^2 versus ≥ 30 to < 45 mL/min/1.73 m^2 versus ≥ 45 to < 60 mL/min/1.73 m^2 versus ≥ 60 to < 75 mL/min/1.73 m^2 versus ≥ 75 mL/min/1.73 m^2), region (North America versus Europe versus Japan versus Asia, other), and UACR at the time of screening (< 20 mg/g versus ≥ 20 to < 200 mg/g versus ≥ 200 to < 500 mg/g versus ≥ 500 to < 1000 mg/g versus ≥ 1000 mg/g).

Treatment with empagliflozin was in compliance with the recommendations of the SPC [9]. In addition, patients in both study arms were to receive individualized standard treatment from their treating physician, taking into account cardiovascular risk factors and existing comorbidities (e.g. high blood pressure, diabetes) and in accordance with local, national, or international guidelines. The discussion on the implementation of the ACT can be found below.

The EMPA-KIDNEY study was event-driven and was to end after 1070 events of the primary outcome. Due to treatment benefits found for empagliflozin, the study was terminated prematurely after reaching 624 events at the time of the planned interim analysis.

The primary outcome of the study was a composite outcome of progression of kidney disease and cardiovascular mortality. Patient-relevant outcomes were recorded in the categories of mortality, morbidity, and side effects.

EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved studies

The 3 studies EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved are placebo-controlled RCTs on empagliflozin which had already been presented by the company in other benefit assessment procedures: the EMPA-REG OUTCOME study in the therapeutic indication of diabetes mellitus type 2 [10], the EMPEROR-Reduced study in the therapeutic indication of symptomatic chronic heart failure with reduced ejection fraction [11], and the EMPEROR-Preserved study in the therapeutic indication of symptomatic chronic heart failure with preserved ejection fraction [12]. The respective information on study design and the characteristics of the corresponding overall populations of the studies are presented in detail for the EMPA-REG OUTCOME study in dossier assessment A16-12 [13], for the EMPEROR-

Reduced study in dossier assessment A21-93 [14], and for the EMPEROR-Preserved study in dossier assessment A22-39 [15].

For reasons of completeness and transparency, the company reports having formed subpopulations from the 3 studies mentioned above based on the diagnostic criteria of the KDIGO guideline [16] and presents the results as supplementary information. The criterion used was an eGFR < 60 mL/min/1.73 m^2 and/or a UACR ≥ 30 mg/g. It is unclear whether these criteria had already been met for at least 3 months by all these patients (as required by the KDIGO for the diagnosis of CKD). For the EMPA-REG OUTCOME study, the company considered only the placebo arm and the study arm in which participants received a dose of 10 mg empagliflozin per day, which was in line with the SPC for this therapeutic indication. The company's classification results in a subpopulation with 2359 patients (1171 in the intervention arm and 1188 in the comparator arm) from the EMPA-REG OUTCOME study and a subpopulation of 6610 patients (3331 in the intervention arm and 3279 in the comparator arm) from the EMPEROR-Reduced and EMPEROR-Preserved studies which were combined by the company in the form of a metaanalysis.

ACT specified by the G-BA not implemented

As the ACT in the present therapeutic indication, the G-BA has specified optimized standard therapy for CKD treatment, taking into account the underlying disease and common comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia). According to current medical knowledge (also see Section I 2), the treatment of CKD is assumed to involve not only ACE inhibitors or AT-1 antagonists, but also the use of SGLT2 inhibitors (in particular dapagliflozin), provided that they are therapeutically indicated for concomitant diseases or the underlying disease as per their marketing authorizations. However, the EMPA-KIDNEY study and the 3 supplementary studies submitted by the company did not allow the use of SGLT2 inhibitors in principle, except as study medication in the intervention arm. In all 4 studies, the prohibition of SGLT2 inhibitors (except in the studies' intervention arms) prevented the treatment of CKD taking into account the underlying disease and common comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) as in the optimized standard therapy required per ACT. The EMPA-KIDNEY study submitted by the company and the supplementary data presented by the company on subpopulations of the EMPA-REG OUTCOME, EMPEROR-Reduced, and EMPEROR-Preserved studies are therefore unsuitable for assessing added benefit in the present research question because the ACT has not been implemented.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of empagliflozin in comparison with the ACT in adults with CKD. There was no hint of an added benefit of empagliflozin in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of empagliflozin in comparison with the ACT is summarized in Table 5.

Table 5: Empagliflozin – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with CKD	Optimized standard therapy for CKD, taking into account the underlying illness and common comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia)[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:
- The present guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association (AkdÄ) in accordance with § 35a (7), sentence 4 SGB V list both approved and unapproved drug therapies for the treatment of CKD. According to the BSG comments on the judgement dated 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered ACTs in the narrower sense of § 2 (1), sentence 3, § 12 SGB V.
- According to current medical knowledge, the treatment of CKD presumably involves not only the use of ACE inhibitors or AT-1 antagonists, but also the use of SGLT2 inhibitors (in particular dapagliflozin), provided that they are therapeutically indicated for concomitant diseases or the underlying disease as per their marketing authorizations. The addition of SGLT2 inhibitors (in particular dapagliflozin) is based on the change in the ACT in the G-BA decisions on finerenone dated 17 August 2023.
- Within the framework of the ACT, it is assumed that patients in both treatment arms receive individualized treatment of the underlying disease and any comorbidities in accordance with current medical knowledge and avoiding the use of nephrotoxic drugs. The approval and dosing information of the drugs' SPCs must be adhered to, and any deviations justified separately.
- Placebo or the unchanged continuation of an inadequate treatment of the underlying disease does not correspond to an ACT if there are still further options for treatment optimization.
- For the target population to be treated, target values for comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) are to be defined before the start of the study; participants should reach these target values before the start of the study or, if applicable, during a run-in phase and maintain them during the study by means of individualized treatment (e.g. dose adjustments). The target values should be based on the treatment standards of the corresponding diseases and, if applicable, take multiple comorbidities into account.
- It is assumed that the treatment goal for the patients in the planned therapeutic indication remains to be a slowdown of disease progression, i.e. renal replacement therapy in the form of dialysis or transplantation is not yet indicated for the patients.

ACE: angiotensin-converting enzyme; ACT: appropriate comparator therapy; AkdÄ: Drug Commission of the German Medical Association; AT-1: angiotensin-1; BSG: Federal Social Court; CKD: chronic kidney disease; G-BA: Joint Federal Committee; SGB: German Social Code; SGLT2: sodium-dependent glucose transporter-2

The assessment described above deviates from that by the company, which derived proof of a considerable added benefit based on the EMPA-KIDNEY study.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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