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
Dapagliflozin (new therapeutic indication: chronic kidney disease)

of 17 February 2022

Contents

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1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient dapagliflozin (Forxiga) was listed for the first time on 15 November 2012 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 5 August 2021, Forxiga 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 amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 26 August 2021, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure

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(VerfO) of the G-BA on the active ingredient dapagliflozin with the new therapeutic indication (adult patients with chronic kidney disease).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 December 2021, 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 dapagliflozin 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, and the addendum to the benefit assessment prepared by the 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 dapagliflozin.

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 Dapagliflozin (Forxiga) according to product information

Forxiga is indicated in adults for the treatment of chronic kidney disease.

Therapeutic indication of the resolution (resolution of 17.02.2022):

See new therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with chronic kidney disease without symptomatic, chronic heart failure as a comorbidity

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

b) Adults with chronic kidney disease with additional symptomatic, chronic heart failure as a comorbidity

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

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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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 Federal Joint Committee has already determined the patient-relevant advantage 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. No medicinal products are specifically approved for the treatment of kidney disease.

The medicinal products approved in the respective indications are used for the treatment of the underlying diseases of kidney disease and common comorbidities such as diabetes mellitus, hypertension, dyslipoproteinaemia and anaemia.

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

on 3. In the present therapeutic indication, no resolutions are to be considered in the context of the determination as appropriate comparator therapy.

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 therapeutic indication.

The G-BA understands the present indication as a complex of chronic kidney disease and diseases involved in its development or contributing to its progression (diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia). In accordance with national and international guidelines, the G-BA considers patient-individual treatment to be appropriate, taking into account the type and severity of the comorbidities present. ACE inhibitors and AT-1 antagonists play an important role in this therapeutic complex in the context of patient-individual therapy, since a positive influence on the progression of kidney disease has been demonstrated for these product classes.

According to the current state of medical knowledge, it is assumed that treatment of chronic kidney disease includes the use of ACE inhibitors or AT-1 antagonists, if they are eligible and not contraindicated or intolerable. Thus, ACE inhibitors or AT-1 antagonists are to be used (in the treatment setting of the add-on therapy) in both study arms.

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Within the framework of the appropriate comparator therapy, it is assumed that a patient-individual treatment of the underlying disease and any comorbidities that may be present is carried out in accordance with the current state of medical knowledge, while avoiding the use of nephrotoxic agents in both treatment arms. There is a discrepancy between agents recommended in the guidelines for the treatment of chronic kidney disease and approved active ingredients.

Placebo or the unchanged continuation of an inadequate therapy of the underlying disease does not correspond to an 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.

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 included for the patients to determine the appropriate comparator therapy.

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 for both patient populations a) and b) as the appropriate comparator therapy, taking into account the underlying disease and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia).

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 dapagliflozin is assessed as follows:

a) Adults with chronic kidney disease without symptomatic chronic heart failure as a comorbidity

Hint of a considerable additional benefit

b) Adults with chronic kidney disease with additional symptomatic, chronic heart failure as a comorbidity

Hint for a minor additional benefit

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Justification:

For the assessment of the additional benefit of dapagliflozin, the pharmaceutical company submits the DAPA-CKD study and supportively a meta-analysis, based on individual patient data of the DAPA-CKD study and sub-populations with kidney disease of the DAPA-HF and DECLARE-TIMI 58 studies. In addition, the pharmaceutical company submits a further meta-analysis with the renal safety studies DELIGHT, DERIVE and MB102029.

DAPA-CKD

The DAPA-CKD study is a placebo-controlled, double-blind, randomised study in which 4,304 patients with chronic kidney disease with an eGFR of ≥ 25 to ≤ 75 ml/min/1.73 m^2 and albuminuria (UACR: ≥ 200 to ≤ 5000 mg/g) were enrolled. Patients should receive individual standard therapy for kidney disease as well as comorbidities in addition to study medication and be treated with a maximally tolerated and stable dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least 4 weeks prior to enrolment in the study.

There was 1:1 randomisation to the two study arms (dapagliflozin or placebo), stratified by the presence of type 2 diabetes mellitus and UACR (≤ 1,000 mg/g vs > 1,000 mg/g). In the study, patients in both study arms received individualised therapy for kidney disease and comorbidities.

The primary endpoint of the DAPA-CKD study is the combined endpoint of sustained reduction in eGFR by ≥ 50%, end-stage renal disease (ESRD), cardiovascular death and renal death. The study was event-driven and was stopped early due to significant treatment advantages of dapagliflozin after 33 months. After the end of the study, all endpoints should be followed up for up to 6 weeks. Patients who discontinued the study medication prematurely were further observed and also followed up for up to 6 weeks after the end of the study. Overall, the treatment duration of just under 27 months and also the observation periods for the individual endpoints are comparable in both study arms.

Patient characteristics are comparable between the treatment arms: On average, the patients in the DAPA-CKD study were 62 years old and predominantly male. 68% of the patients were diagnosed with type 2 diabetes mellitus, while 11% with heart failure at the time of enrolment in the study. Median eGFR in patients was 41 (intervention arm) and 42 ml/min/1.73m^2 (comparator arm), and UACR was 965 mg/g and 934 mg/g, respectively.

Implementation of the appropriate comparator therapy in the DAPA-CKD study

An optimised standard therapy for the treatment of chronic kidney disease, taking into account the underlying disease and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia), was determined as the appropriate comparator therapy.

In the study, patients were to receive patient-individual standard therapy according to local guidelines for the treatment of both kidney disease and other comorbidities such as cardiovascular disease or type 2 diabetes mellitus. According to the inclusion criteria, treatment of all patients with ACE inhibitors or ARBs at a maximum tolerated dose ≥ 4 weeks prior to enrolment in the study had to be proven. In the further course of the study, there were no limitations regarding the adjustment of the background therapy (change of therapy or dose adjustments).

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According to guideline-based treatment of chronic kidney disease[2], the causes should be treated, the disease progression slowed down as well as comorbidities treated. Patients with an eGFR < 60 ml/min/1.73 m^2 and a blood pressure of > 140/90 mmHg should therefore be offered measures to lower their blood pressure. In addition, patients with proteinuria and/or diabetes without elevated blood pressure are also recommended treatment with ACE inhibitors or ARBs for inhibition of disease progression. In the DAPA-CKD study, 97% of patients received treatment with ACE inhibitors or ARBs at the start of the study. Elevated glycated haemoglobin (HbA1c) levels in patients with diabetes and elevated blood pressure increase the risk of progression to kidney disease. Approximately 94% of the patients received a therapy for the treatment of type 2 diabetes mellitus at the start of the study, the mean HbA1c was 7.8% in both treatment groups. In addition, the systolic blood pressure in both groups, with an average value of 137 mmHg at the start of the study, which did not change significantly during the course of the study, was not within the target range for patients with CKD according to the current KDIGO guideline. From the data submitted by the pharmaceutical company during the written statement procedure, it emerges that in the DAPA-CKD study, approximately 50% of the patients received an adjusted CKD medication in the course of the study. However, there is no information available on the reasons why therapy was or was not adjusted or changed, and whether it was a new initiation, dose increase or dose reduction.

The DAPA-CKD study is used for the benefit assessment despite these remaining uncertainties regarding the implementation of the appropriate comparator therapy.

DAPA-HF

The DAPA-HF study is a placebo-controlled, double-blind, randomised study that enrolled 4,744 patients with symptomatic NYHA class II to IV heart failure with reduced ejection fraction, defined as left ventricular ejection fraction (LVEF) ≤ 40%, who were treated with unmodified, optimised standard therapy for heart failure for at least 4 weeks prior to enrolment in the study. This standard therapy should include, unless contraindicated, ACE inhibitors, ARB or sacubitril/valsartan in combination with a beta-blocker and, if appropriate, an MRA4.

There was a 1:1 randomisation to the two study arms (dapagliflozin or placebo), with stratification according to the concomitant presence of type 2 diabetes mellitus. In the study, patients in both study arms received individually adapted therapy for heart failure as well as for other comorbidities such as type 2 diabetes mellitus.

The primary endpoint of the DAPA-HF study is the combined endpoint of cardiovascular death, hospitalisation due to heart failure, and emergency medical contact due to heart failure. The study was event-driven and was to be terminated after 844 events of the primary endpoint, and all endpoints were to be followed up for up to 6 weeks. Patients who discontinued study medication early after randomisation were also followed up for up to 6 weeks after the end of the study. Overall, the treatment duration of just under 18 months and also the observation periods for the individual endpoints are comparable in both study arms.

[2] German Society of General Practice/Family Medicine. Care of patients with chronic kidney disease without dialysis requirement in general practice; S3 guideline. 2019.

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Relevant sub-population of the DAPA-HF study

The relevant sub-population (CKD sub-population) consists of patients with chronic kidney disease with eGFR < 60 ml/min/1.73 m^2, who make up about 41% of the total population of the DAPA-HF study. In the DAPA-HF study, no values were collected for UACR and therefore no information is available on the percentage of patients with albuminuria in this study.

The patient characteristics of the CKD sub-population of the DAPA-HF study are comparable between the treatment arms: On average, the patients were 71 years old and predominantly male. 48% of the patients were diagnosed with type 2 diabetes mellitus at the time of enrolment in the study. The median eGFR in the patients was 48 ml/min/1.73 m^2.

Implementation of the appropriate comparator therapy in the DAPA-HF study

An optimised standard therapy for the treatment of chronic kidney disease, taking into account the underlying disease and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia), was determined as the appropriate comparator therapy.

In the DAPA-HF study, patients were to receive patient-individual standard therapy according to local guidelines for heart failure, cardiovascular risk factors and type 2 diabetes mellitus. According to the study protocol, therapy adjustments were possible at any time during the course of the study, but therapy should be optimised ≥ 4 weeks before time of enrolment and kept as stable as possible.

At the start of the DAPA-HF study, approximately 81% of patients in the CKD sub-population received treatment with ACE inhibitors or ARBs, approximately 95% received treatment with beta-blockers and approximately 11% received treatment with sacubitril/valsartan. No data are available for mineralocorticoid receptor antagonists (MRAs) in the CKD sub-population, but in the total population approximately 71% received additional MRAs. Approximately 81% of the patients in the CKD sub-population were receiving treatment for type 2 diabetes mellitus at the start of the study; the mean HbA1c in both treatment groups was 6.6%. From the data submitted by the pharmaceutical company during the written statement procedure, it emerges that in the CKD sub-population of the DAPA-HF study, approximately 60% of the patients received an adjusted CKD medication in the course of the study. However, there is no information available on the reasons why therapy was or was not adjusted or changed, and whether it was a new initiation, dose increase or dose reduction.

There is also uncertainty as to whether there was a change of therapy to sacubitril/valsartan in other patients. According to the guideline recommendations for heart failure[3], a change of therapy to sacubitril/valsartan (angiotensin receptor neprilysin inhibitor, ARNI) is recommended for patients who show symptoms despite guideline-compliant therapy with ACE inhibitors or ARBs, beta-blockers and MRAs. However, due to the current uncertainties regarding the difficulties in the change phase and the side effect profile in these patients, special attention should be paid to contraindications and intolerances, which can occur to an even greater extent in patients with kidney disease according to the product information on sacubitril-valsartan.

The DAPA-CKD study is used for the benefit assessment despite these remaining uncertainties regarding the implementation of the appropriate comparator therapy.

[3]NVL heart failure (https://www.leitlinien.de/nvl/html/nvl-chronische-herzinsuffizienz/3-auflage/kapitel-6#section-1)

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DECLARE-TIMI 58

The DECLARE-TIMI 58 study is a randomised, double-blind, placebo-controlled, two-arm study that enrolled patients with type 2 diabetes mellitus who were at high cardiovascular risk. The study also enrolled patients with chronic kidney disease with eGFR < 60 ml/min/1.73 m^2 and/or UACR > 30 mg/g, representing 34% of the total population. However, approximately 80% of patients in this sub-population show an eGFR > 60 ml/min/1.73 m^2. It can be deduced that the renal function of the CKD sub-population of the DECLARE-TIMI 58 study is not as severely impaired as in the populations of the DAPA-CKD and DAPA-HF studies.

The DECLARE-TIMI 58 study is not used for the benefit assessment of dapagliflozin in chronic kidney disease because the adequate implementation of the G-BA's appropriate comparator therapy is questionable for the CKD sub-population in this study and no relevant statements can be obtained beyond the results of the DAPA-CKD and DAPA-HF studies.

According to the appropriate comparator therapy, both kidney disease and comorbidities should be treated optimally according to the state of medical knowledge. According to the current National Health Care Guideline for type 2 diabetes mellitus[4], patients with type 2 diabetes mellitus and concomitant cardiovascular disease or high cardiovascular risk should also be offered sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists (e.g., liraglutide). Although the target value should be determined patient-individually, a target value range for blood glucose control based on the HbA1c value of <8.0% should generally be aimed for. However, the treatment of CKD patients with type 2 diabetes mellitus in the comparator arm of the DECLARE-TIMI 58 study did not comply with the currently valid recommendations, as treatment with SGLT2 inhibitors was not allowed and liraglutide was hardly used. Thus, the treatment in the comparator arm of this study did not comply with the therapy algorithm of the current National Health Care Guideline for type 2 diabetes mellitus. Treatment with SGLT2 inhibitors was also excluded in the DAPA-CKD and DAPA-HF studies. According to the product information(s) for the SGLT-2 inhibitors (e.g., empagliflozin[5]), the blood glucose-lowering efficacy of SGLT-2 inhibitors is reduced in patients with moderate renal impairment and is probably absent in patients with severe renal impairment. In about 90% of the patients in the DAPA-CKD study and in the entire CKD sub-population of the DAPA-HF study, the eGFR values were below 60 ml/min/1.73 m^2, so that the treatment option of an SGLT-2 inhibitor has a significantly lower value in these patients than in patients with an eGFR > 60 ml/min/1.73 m^2, as was the case in a clear majority of the CKD patients in the DECLARE-TIMI 58 study. In addition, in contrast to the DECLARE-TIMI 58 study, the DAPA-CKD and DAPA-HF studies achieved comparable high HbA1c values in both study arms in the course of the study which were consistently within the target range for blood glucose control (HbA1c <8.0%). For the DAPA-CKD and DAPA-HF studies, it can therefore be assumed that the implementation of the appropriate comparator therapy with regard to type 2 diabetes mellitus is at least basically sufficient, even without the option of treatment with SGLT2 inhibitors.

For the DECLARE-TIMI 58 study, such major deficiencies are seen overall with regard to the implementation of CRVO in the present therapeutic indication that no relevant statements can be obtained for the present research question beyond the results of the DAPA-CKD and the DAPA-HF studies. Irrespective of the question of the fundamental applicability of the DECLARE-TIMI 58 study for the present research question, this study, like the DAPA-CKD study

[4] German Medical Association (BÄK), National Association of Statutory Health Insurance Physicians (KBV), Association of the Scientific Medical Societies (AWMF): National Health Care Guideline: Type 2 diabetes mellitus: https://www.leitlinien.de/themen/diabetes/pdf/diabetes-2aufl-vers1.pdf (last access: 10 December 2021). AWMF Reg. No.: nvl-001. – long version. 2nd edition, version 1: ÄZQ 2021.

[5] https://www.ema.europa.eu/en/documents/product-information/jardiance-epar-product-information_en.pdf

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for the most part, investigates a population with type 2 diabetes mellitus as the underlying disease. The results of the DAPA-CKD study are confirmed overall, but no significant additional results are provided, so that it is refrained from further discussion of the results of DECLARE-TIMI 58 study.

Renal safety studies DELIGHT, DERIVE and MB102029

The renal safety studies *DELIGHT, DERIVE and MB102029* submitted additionally by the pharmaceutical company, which included patients with kidney disease and type 2 diabetes mellitus, are not relevant for the present assessment due to the lack of implementation of the appropriate comparator therapy, and are therefore not considered.

On the division of the patient population

The patient populations of the DAPA-CKD study and the CKD sub-population of the DAPA-HF study differ in several relevant respects.

On the one hand, there are different baseline risks with regard to the patient characteristics of age, albuminuria and eGFR. The patients in the CKD sub-population of the DAPA-HF study are on average about 10 years older, the percentage of patients with albuminuria is not known due to the non-recording of the UACR, and there are significantly fewer patients in percentage terms with an eGFR < 45 ml/min/1.73 m^2 at baseline. The comorbidities are also distributed differently between the patient populations: about 68% of the patients in the DAPA-CKD study have been diagnosed with type 2 diabetes mellitus, whereas in the CKD sub-population of the DAPA-HF study it is only 48%. In the DAPA-CKD study, only 11% of the patients have chronic heart failure; in the DAPA-HF study, in contrast, all patients have chronic heart failure, as the DAPA-HF study is the marketing authorisation study in the indication of chronic heart failure.

In contrast, there are different results in the effect estimators of the endpoints. For example, patients in the CKD sub-population of the DAPA-HF study have a 3-fold higher mortality and a 5-fold lower event rate for the renal endpoint of ESRD. It can be deduced that the patients in the CKD sub-population of the DAPA-HF study have a significantly higher disease burden than the patients in the DAPA-CKD study. Thus, more specific statements on the additional benefit of treatment with dapagliflozin in patients with the comorbidity of heart failure can be derived from this patient population.

Due to the differences described in the DAPA-CKD and DAPA-HF studies, the additional benefit for adults with chronic kidney disease cannot be derived by considering the studies together. Against this background, two patient groups are distinguished on the basis of the comorbidity heart failure: a) adults with chronic kidney disease without symptomatic, chronic heart failure as a comorbidity and b) adults with chronic kidney disease with additional symptomatic, chronic heart failure as a comorbidity.

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a) Adults with chronic kidney disease without symptomatic chronic heart failure as a comorbidity

Extent and probability of the additional benefit

Mortality

Overall mortality
In the DAPA-CKD study, statistically significantly fewer patients died in the dapagliflozin arm compared to the control arm.

Morbidity

Renal morbidity
Renal morbidity was assessed by a combined endpoint consisting of the individual endpoints of confirmed sustained reduction of eGFR by ≥ 50%, ESRD and renal death. For the assessment, only the ESRD endpoint is used and the broader combined endpoint of renal morbidity as a whole is presented additionally.

Sustained reduction of eGFR by ≥ 50%
Within the G-BA, there are different opinions on whether renal function measured by eGFR represents a per se patient-relevant endpoint.
Similarly, there are differing opinions as to whether the sustained reduction of eGFR by ≥ 50% in the present case constitutes a patient-relevant endpoint.
The endpoint of confirmed sustained reduction of eGFR by ≥ 50% is therefore only presented additionally.

Renal death
Due to competing events, e.g., with cardiac causes of death (see endpoint "overall mortality"), the separate consideration of the endpoint "renal death" is considered inappropriate and the endpoint is only presented additionally.

ESRD
The combined endpoint of end-stage renal disease (ESRD) includes the individual components of sustained eGFR < 15 ml/min/1.73 m^2, chronic dialysis treatment and receipt of a kidney transplant. The significance of the individual component "receipt of a kidney transplant" is questionable, since the availability of organs is to be regarded as very heterogeneous, depending on the study location.
There were statistically significant advantages of dapagliflozin for the combined endpoint as well as for the two individual components "eGFR < 15 ml/min/1.73 m^2" and "chronic dialysis treatment". For the single component "receipt of a kidney transplant", there was no statistically significant difference between the treatment arms, but only very few events occurred in each case.

Reaching CKD stage 4
Reaching CKD stage 4 is patient-relevant. However, only patients who had an eGFR ≥ 40 ml/min/1.73 m^2 at randomisation are included in the present evaluation of the endpoint in the DAPA-CKD study. Since this only applies to about 50% of the patients in the DAPA-CKD study, this evaluation does not allow any statement about the total study population and is therefore not used for assessment.

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Total hospitalisations
For the endpoint "total hospitalisations", statistically significantly fewer hospitalisations occurred in the dapagliflozin arm compared to the control arm in the DAPA-CKD study.

Myocardial infarction
For the combined endpoint "myocardial infarction", consisting of the individual components "non-fatal myocardial infarction" and "fatal myocardial infarction", there are no statistically significant differences between the treatment arms.

Stroke
For the combined endpoint "stroke", consisting of the individual components "non-fatal stroke" and "fatal stroke", there are 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 deterioration of ≥ 15 points, there is a statistically significant difference to the advantage of dapagliflozin compared to the comparator arm. However, this difference is no more than minor.

Quality of life

Kidney Disease Quality of Life (KDQOL-36)
The KDQOL-36 is an instrument for assessing disease-specific quality of life in kidney disease. It consists of two subscales of the generic questionnaire SF-12 and three disease-specific subscales for the assessment of kidney disease:

- Physical subscale of the SF-12 (PCS)
- Mental subscale of the SF-12 (MCS)
- Burden of kidney disease
- Symptoms/problems of kidney disease
- Effects of kidney disease on daily life

For the evaluation, the answers of each subscale were transformed into scores between 0 (conceivably worst quality of life) and 100 (conceivably best quality of life).

For the subscale "impact of kidney disease on daily life", the DAPA-CKD study shows a significant difference to the advantage of dapagliflozin compared to the control arm. This showed an effect modification for the gender characteristic (positive effect only for women), which is nevertheless not relevant to the conclusion.
For other subscales "physical subscale (PCS)", "mental subscale (MCS)", as well as "Burden of kidney disease" and "symptoms/problems of kidney disease", there were no statistically significant differences between the treatment arms.

Side effects

In the DAPA-CKD study, there was no systematic assessment of adverse events (AEs) regardless of severity grade. Only non-serious AEs that led to therapy discontinuation or dose adjustment or belonged to a selection of AEs predefined by the pharmaceutical company were recorded. This approach may mean that common, patient-relevant non-serious AEs are not systematically identified in the study.

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Serious adverse events (SAE)
For the endpoint SAE, the DAPA-CKD study showed a statistically significant difference to the advantage of dapagliflozin compared to the control arm. This showed an effect modification for the age characteristic (positive effect only for those ≤ 65 years of age), which is nevertheless not relevant to the conclusion.

Discontinuation due to AEs
For the endpoint of discontinuation due to AEs, no statistically significant difference was detected between the treatment arms in the DAPA-CKD study.

Specific AEs
Genital and urinary tract infections
The AEs belonging to the genital and urinary tract infection complexes are not listed as AEs of special interest (AESI) in the study protocols. It can therefore be assumed that non-serious AEs were not fully assessed. The data on these AEs are not usable since primarily non-serious genital and urinary tract infections are not to be expected in the therapeutic indication.

Diabetic ketoacidosis
Diabetic ketoacidosis occurred in only 2 (0.1%) patients in the comparator arm and there was no event in the dapagliflozin arm. However, there was no statistically significant difference between the treatment groups for this endpoint.

Pneumonia and metabolism and nutrition disorders
For the endpoints "pneumonia" and "metabolism and nutrition disorders", the DAPA-CKD study showed a statistically significant difference to the advantage of dapagliflozin compared to the control arm.

Overall assessment
For the benefit assessment, the placebo-controlled, double-blind, randomised DAPA-CKD study is available, which investigated the efficacy and safety of dapagliflozin compared to placebo (in each case in addition to optimal standard therapy for kidney disease) over approximately 33 months in patients with chronic kidney disease with an eGFR of ≥ 25 to ≤ 75 ml/min/1.73 m^2 and albuminuria (UACR: ≥ 200 to ≤ 5,000 mg/g).

In the mortality category, the endpoint "overall mortality" shows a statistically significant advantage of dapagliflozin compared to the control arm.

In the morbidity category, there was a statistically significant advantage of dapagliflozin for the combined endpoint ESRD and the individual components eGFR < 15 ml/min/1.73 m^2 and chronic dialysis treatment.

The results on the avoidance of total hospitalisations support the outcome.

In terms of health status, as assessed by the EQ-5D VAS, the deterioration by ≥ 15 points shows a statistically significant advantage of dapagliflozin compared to the control arm, but this is no more than minor.

For the other endpoints in the category of morbidity, myocardial infarction and stroke, there are no statistically significant differences between the treatment arms.

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In the category of health-related quality of life, only one subscale of the KDQOL-36 questionnaire ("effects of kidney disease on daily life") showed statistically significant advantages of dapagliflozin. In all other four subscales, there were no statistically significant differences between the treatment arms.

In the category of side effects, it should be noted that there was no systematic assessment of AEs, independent of the severity grade, in the DAPA-CKD study. Only non-serious AEs that led to therapy discontinuation or dose adjustment or belonged to a selection of AEs predefined by the pharmaceutical company were recorded. There were statistically significant advantages of dapagliflozin for SAEs, as well as in detail for the specific AEs pneumonia and metabolism and nutrition disorders. For the endpoint "diabetic ketoacidosis", no statistically significant difference was detected between the treatment arms.

In the overall assessment of the results based on the positive effects of dapagliflozin in the endpoint categories of mortality, morbidity (ESRD, total hospitalisations) as well as side effects (SAEs, and in detail the specific AEs), a considerable additional benefit of dapagliflozin compared to the appropriate comparator therapy is derived overall.

Reliability of data (probability of additional benefit)

Overall, the DAPA-CKD study shows uncertainties that limit the significance of the results.
For the implementation of the appropriate comparator therapy, there are uncertainties about the extent to which all optimisation options were exhausted in the study, if a therapy adjustment was indicated.

Further uncertainties arise from the fact that no patients with an albuminuria with UACR < 200mg/g were enrolled in the DAPA-CKD study.

Furthermore, due to the lack of a systematic assessment of AEs, side effects cannot be fully assessed regardless of severity grade. Data on non-serious AEs are missing, as only non-serious AEs were recorded that led to therapy discontinuation or dose adjustment or belonged to a selection of AEs predefined by the pharmaceutical company.

Against the background of these uncertainties, the reliability of data is therefore classified as "hint".

b) Adults with chronic kidney disease with additional symptomatic, chronic heart failure as a comorbidity

Extent and probability of the additional benefit

Mortality

For the endpoint "overall mortality", there was no statistically significant difference between the treatment arms in the CKD sub-population of the DAPA-HF study.

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Morbidity

Renal morbidity
Renal morbidity was assessed by a combined endpoint consisting of the individual endpoints of confirmed sustained reduction of eGFR by ≥ 50%, ESRD and renal death. The combined endpoint ESRD is used for the assessment and the broader combined endpoint on overall renal morbidity is presented additionally. For the combined endpoint, there were no statistically significant differences between the treatment arms.

Sustained reduction of eGFR by ≥ 50%
Within the G-BA, there are different opinions on whether renal function measured by eGFR represents a per se patient-relevant endpoint.
Similarly, there are differing opinions as to whether the sustained reduction of eGFR by ≥ 50% in the present case constitutes a patient-relevant endpoint. The overall statement on the extent of the additional benefit remains unaffected. For the endpoint, there were no statistically significant differences between the treatment arms.

Renal death
Due to competing events, e.g. with cardiac causes of death (see endpoint "overall mortality"), the separate consideration of the endpoint "renal death" is considered inappropriate and the endpoint is only presented additionally. There were no statistically significant differences between the treatment arms.

ESRD
The combined endpoint of end-stage renal disease (ESRD) includes the individual components of sustained eGFR < 15 ml/min/1.73 m^2, chronic dialysis treatment and receipt of a kidney transplant. The significance of the individual component "receipt of a kidney transplant" is questionable, since the availability of organs is to be regarded as very heterogeneous, depending on the study location. For the combined endpoint as well as the individual components, there were no statistically significant differences between the treatment arms.

Total hospitalisations
For the endpoint "total hospitalisation", statistically significantly fewer hospitalisations occurred in the dapagliflozin arm compared to the control arm in the CKD sub-population of the DAPA-HF study.

Myocardial infarction
For the combined endpoint "myocardial infarction", consisting of the individual components "non-fatal myocardial infarction" and "fatal myocardial infarction", there are no statistically significant differences between the treatment arms.

Stroke
For the combined endpoint "stroke", consisting of the individual components "non-fatal stroke" and "fatal stroke", there are 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, there was no statistically significant difference between the treatment arms.

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Quality of life

In the DAPA-HF study, only heart failure disease-specific quality of life was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The pharmaceutical company did not submit the KCCQ evaluations for the CKD sub-population of the DAPA-HF study. Accordingly, no statements can be derived on the quality of life.

Side effects

In the DAPA-HF study, there was no systematic assessment of adverse events (AEs) regardless of severity grade. Only non-serious AEs that led to therapy discontinuation or dose adjustment or belonged to a selection of AEs predefined by the pharmaceutical company were recorded. This approach may mean that common, patient-relevant non-serious AEs are not systematically identified in the study.

Serious adverse events (SAE)
For the endpoint SAE, there was a statistically significant difference to the advantage of dapagliflozin compared to the control arm in the CKD sub-population of the DAPA-HF study.

Discontinuation due to AEs
For the endpoint of discontinuation due to AEs, there was no statistically significant difference between the treatment arms in the CKD sub-population of the DAPA-HF study.

Specific AEs
Genital and urinary tract infections
The AEs belonging to the genital and urinary tract infection complexes are not listed as AEs of special interest (AESI) in the study protocols. It can therefore be assumed that non-serious AEs were not fully assessed. The data on these AEs are not usable since primarily non-serious genital and urinary tract infections are not to be expected in the therapeutic indication.

Diabetic ketoacidosis
Diabetic ketoacidosis did not occur in the CKD sub-population of the DAPA-HF study in either treatment arm.

Noncardiac chest pain and respiratory, thoracic and mediastinal disorders
For the endpoints "noncardiac chest pain" and "respiratory, thoracic and mediastinal disorders", there was a statistically significant difference to the advantage of dapagliflozin compared to the control arm in the CKD sub-population of the DAPA-HF study.

Overall assessment

For the benefit assessment, the placebo-controlled, double-blind, randomised study DAPA-HF is available, which investigated the efficacy and safety of dapagliflozin compared to placebo (in each case in addition to optimal standard therapy for heart failure) over approximately 18 months in patients with symptomatic heart failure of NYHA class II to IV with reduced ejection fraction. The relevant sub-population (CKD sub-population) consists of patients with chronic kidney disease with eGFR < 60 ml/min/1.73 m^2, who make up 41% of the total population of the DAPA-HF study

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In the mortality category, for the endpoint "overall mortality", there are no statistically significant differences between treatment arms.

In the morbidity category, for the combined endpoint ESRD and the individual components, there are no statistically significant differences between the treatment arms.

For the endpoint "total hospitalisation", there were statistically significant advantages of dapagliflozin.

There were no statistically significant differences between the treatment arms in terms of improvement by ≥ 15 points in health status as assessed by the EQ-5D VAS.

For the other endpoints in the category of morbidity, myocardial infarction and stroke, there are no statistically significant differences between the treatment arms.

In the category of side effects, it should be noted that there was no systematic assessment of AEs, independent of the severity grade, in the DAPA-HF study. Only non-serious AEs that led to therapy discontinuation or dose adjustment or belonged to a selection of AEs predefined by the pharmaceutical company were recorded. There were statistically significant advantages of dapagliflozin for the endpoint SAEs, as well as for the specific AEs "noncardiac chest pain" and "respiratory, thoracic and mediastinal disorders". For the endpoint "diabetic ketoacidosis", there is no statistically significant difference between the treatment arms since no events occurred.

In the overall assessment of the results based on the positive effects of dapagliflozin in the avoidance of total hospitalisations as well as in the advantages in the category of side effects (SAE), a minor additional benefit of dapagliflozin compared to the appropriate comparator therapy is derived overall.

Reliability of data (probability of additional benefit)

Overall, the DAPA-HF study has uncertainties that limit the significance of the results for the CKD sub-population.

The implementation of the appropriate comparator therapy is subject to uncertainties, which result in particular from the fact that no detailed information is available on therapy optimisations in the course of the study despite the data subsequently submitted in the written statement procedure, e.g., whether the therapy adjustments involved a new initiation, dose increase or dose reduction.

Further uncertainties arise from the fact that no data are available on the percentage of patients with albuminuria, as the UACR was not measured.

Furthermore, due to the lack of a systematic assessment of AEs, side effects cannot be fully assessed regardless of severity grade. Data on non-serious AEs are missing, as only non-serious AEs were recorded that led to therapy discontinuation or dose adjustment or belonged to a selection of AEs predefined by the pharmaceutical company.

Against the background of these uncertainties, the reliability of data is therefore classified as "hint".

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2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient dapagliflozin. The therapeutic indication assessed here is "Forxiga is indicated in adult patients for the treatment of chronic kidney disease."

In the therapeutic indication to be considered, two patient groups were distinguished:

a) adults with chronic kidney disease without symptomatic, chronic heart failure as a comorbidity
b) adults with chronic kidney disease with additional symptomatic, chronic heart failure as a comorbidity

The G-BA determined "an optimised standard therapy for the treatment of chronic kidney disease, taking into account the underlying disease and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia)" as the appropriate comparator therapy for both patient groups a) and b).

<u>About patient group a)</u>

For this patient group, the DAPA-CKD study is available, which investigated treatment of patients with chronic kidney disease with dapagliflozin in comparison to placebo (in each case in addition to an optimal standard therapy for kidney disease).

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

With regard to morbidity, the endpoints "ESRD" and "total hospitalisation" show statistically significant advantages of dapagliflozin.

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

In the side effects category, there are statistically significant results in favour of dapagliflozin for SAEs and in detail for specific AEs.

Overall, the study shows uncertainties, particularly concerning the implementation of the appropriate comparator therapy with regard to the exhaustion of optimisation possibilities, the exclusion of patients with albuminuria with UACR <200 mg/g and the missing systematic assessments of AEs, regardless of severity grade.

In the overall assessment of the positive effects, taking into account the uncertainties mentioned above, the G-BA found a hint for a considerable additional benefit.

<u>About patient group b)</u>

For this patient group, the results of the CKD sub-population of the DAPA-HF study, which investigated the treatment of symptomatic, NYHA class II to IV heart failure patients with reduced ejection fraction with dapagliflozin in comparison with placebo (in each case in addition to optimal standard therapy), are available.

For the overall mortality, there are no statistically significant differences between the treatment arms.

In the morbidity category, the endpoint "total hospitalisation" shows a statistically significant advantage of dapagliflozin.

In the side effects category, there are statistically significant results in favour of dapagliflozin for SAEs and in detail for specific AEs.

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Overall, the study shows uncertainties, particularly concerning the implementation of the appropriate comparator therapy with regard to the exploitation of optimisation possibilities, the missing data on the percentage of patients with albuminuria and the missing systematic assessments of AEs, regardless of severity grade.

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 (SHI). There is no subdivision into patient populations a) and b) here as no calculations, differentiated according to the comorbidity of heart failure, are available.

The data follow IQWiG's assessment. Uncertainties exist in particular due to the inclusion of all patients in CKD stages 1, 2 and 5. Overall, an overestimation of the number of patients can be assumed.

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 Forxiga (active ingredient: dapagliflozin) at the following publicly accessible link (last access: 12 January 2022):

https://www.ema.europa.eu/en/documents/product-information/forxiga-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: 1 February 2022). The costs are presented together here as the appropriate comparator therapy is the same for both patient populations (adults with chronic kidney disease with or without symptomatic chronic heart failure).

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.

The appropriate comparator therapy "An optimised standard therapy for the treatment of chronic kidney disease, taking into account the underlying disease and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, 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 blockers (ARBs).

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,

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optimised standard therapy for the treatment of symptomatic chronic kidney disease and the underlying diseases is provided both in the context of the drug to be evaluated, dapagliflozin, and in the context 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				
Dapagliflozin	1 x daily	365	1	365
+ optimised standard therapy	Different from patient to patient			
Appropriate comparator therapy				
Patient population a) + b) Adults with chronic kidney disease				
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					
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
+ optimised standard therapy	Different from patient to patient				
Appropriate comparator therapy					
Patient population a) + b)					
Optimised standard therapy	Different from patient to patient				

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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 usage. 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					
Dapagliflozin	98 FCT	€ 158.72	€ 1.77	€ 0.00	€ 156.95
+ optimised standard therapy	Different from patient to patient				
Appropriate comparator therapy					
Patient population a) + b)					
Optimised standard therapy	Different from patient to patient				
Abbreviations: FCT = film-coated tablets					

LAUER-TAXE® last revised: 1 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.

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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 26 July 2016, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. Working group 35a adapted the appropriate comparator therapy at its session on 13 July 2021.

On 25 August 2021, the pharmaceutical company submitted a dossier for the benefit assessment of dapagliflozin to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 27 August 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 dapagliflozin.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 December 2021. The deadline for submitting written statements was 22 December 2021.

The oral hearing was held on 10 January 2022.

By letter dated 11 January 2022, 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 January 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 was discussed at the session of the subcommittee on 8 February 2022, and the proposed resolution was approved.

At its session on 17 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

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Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	26 July 2016	Determination of the appropriate comparator therapy
Working group Section 35a	13 July 2021	Implementation of the appropriate comparator therapy
Working group Section 35a	4 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	10 January 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 January 2022 1 February 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	8 February 2022	Concluding discussion of the draft resolution
Plenum	17 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 17 February 2022

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

Prof. Hecken

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