Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Dapagliflozin (new therapeutic indication: chronic heart failure with left ventricular ejection fraction LVEF > 40%)

of 17 August 2023

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

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

On 3 February 2023, dapagliflozin received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 17 February 2023, i.e. no later than four weeks after the pharmaceutical company has been notified of the authorisation for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in

conjunction with Chapter 5, Section 8, paragraph 1, number 2 sentence 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient dapagliflozin with the new therapeutic indication (chronic heart failure with left ventricular ejection fraction LVEF > 40%).

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

The G-BA came to a resolution on whether an additional benefit of 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 symptomatic chronic heart failure.

Therapeutic indication of the resolution (resolution of 17 August 2023):

Adults with symptomatic chronic heart failure with preserved ejection fraction HFpEF (LVEF > 50%) and with mildly reduced ejection fraction HFmrEF (LVEF > 40 to 49%)

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with symptomatic chronic heart failure with preserved ejection fraction HFpEF (LVEF > 50%) and with mildly reduced ejection fraction HFmrEF (LVEF > 40 to 49%)

Appropriate comparator therapy for dapagliflozin:

An optimised standard therapy for the treatment of symptomatic chronic heart failure with preserved ejection fraction or mildly reduced ejection fraction and the underlying conditions, such as hypertension, arrhythmias, coronary artery heart disease, diabetes mellitus, chronic kidney disease, dyslipoproteinaemia as well as the concomitant symptoms

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

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

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

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

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

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

on 1. The following active ingredients or active ingredients from the following product classes are generally approved for the treatment of chronic heart failure:

- Angiotensin-converting enzyme inhibitors (ACE inhibitors)
- Beta-adrenoceptor antagonists (beta receptor blockers)
- AT1 receptor blockers (ARBs)
- Diuretics
- Mineralocorticoid receptor antagonists (MRA)
- Empagliflozin
- Sacubitril/ valsartan *(only for reduced ejection fraction)*
- Vericiguat *(only for reduced ejection fraction)*

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

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

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

The following resolution is available for the therapeutic indication of chronic heart failure with preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF):

- Empagliflozin (resolution of 15 September 2022)

The following resolutions are available for the therapeutic indication of chronic heart failure with reduced ejection fraction:

- Sacubitril/ valsartan (resolution of 16 June 2016)

- Dapagliflozin (resolution of 20 May 2021)
- Empagliflozin (resolution of 6 January 2022)
- Vericiguat (resolution of 3 March 2022)

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

A distinction is made between different forms of chronic heart failure[2, 3]. Dapagliflozin has already been approved for the treatment of chronic heart failure with reduced ejection fraction and assessed in the early benefit assessment[4]. With the extension of the therapeutic indication available now, dapagliflozin is approved for the treatment of chronic heart failure irrespective of left ventricular ejection fraction (LVEF), and is therefore also indicated in the case of preserved ejection fraction (HFpEF) and mildly reduced ejection fraction (HFmrEF). Accordingly, for the present new therapeutic indication of dapagliflozin, adults with chronic heart failure with preserved ejection fraction and mildly reduced ejection fraction (HFmrEF) (LVEF > 40 to 49%) and thus with an LVEF > 40% overall are considered.

Various active ingredients or product classes are approved for the treatment of heart failure with reduced ejection fraction (HFrEF), such as ACE inhibitors, ARBs, beta-receptor blockers, mineralocorticoid receptor antagonists (MRAs) and others. For the treatment of heart failure with LVEF > 40%, evidence is available for the active ingredient empagliflozin, which was the basis for the extension of the marketing authorisation of empagliflozin for the treatment of heart failure – independent of the ejection fraction, and thus also for HFpEF and HFmrEF.

For empagliflozin, a hint for a minor additional benefit compared with optimised standard therapy for symptomatic chronic heart failure with preserved ejection fraction or mildly reduced ejection fraction and underlying conditions was identified.[5] Empagliflozin is not currently used as a therapy standard in the clinical management of patients with symptomatic chronic heart failure with HFpEF or HFmrEF. Based on the generally accepted state of medical knowledge, empagliflozin is therefore not eligible as a component of the appropriate comparator therapy.

Overall, the body of evidence for the treatment of patients with both HFpEF and HFmrEF is limited. According to the guideline recommendations,[3] patients with HFpEF should be treated for relevant comorbidities, and symptomatic patients with HFmrEF should be treated in the same way as patients with HFrEF.

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. Accordingly, an optimised standard therapy for the treatment of symptomatic, chronic heart failure with preserved ejection fraction or mildly reduced ejection fraction and the underlying diseases, such as hypertension, arrhythmias,

[2] Forxiga – European public assessment report EPAR (Scientific) – Variation https://www.ema.europa.eu/en/documents/variation-report/forxiga-h-c-ws-2299-epar-assessment-report-variation_en.pdf

[3] National Health Care Guideline Heart Failure (2019): https://www.leitlinien.de/nvl/html/nvl-chronische-herzinsuffizienz/3-auflage/kapitel-6#section-1

[4] Resolution on the early benefit assessment of dapagliflozin (chronic heart failure with reduced ejection fraction with LVEF ≤ 40%) of 20.05.2021 https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/615/#beschluesse

[5] Resolution on the early benefit assessment of empagliflozin (chronic heart failure with LVEF > 40%) of 15.09.2022 https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/810/#beschluesse

coronary artery heart disease, diabetes mellitus, chronic kidney disease, dyslipoproteinaemia as well as the concomitant symptoms is determined as the appropriate comparator therapy.

In the pivotal study for the new therapeutic indication, dapagliflozin was administered as an add-on to standard therapy. Therefore, it is anticipated that dapagliflozin will be used in addition to standard therapy for the treatment of symptomatic chronic heart failure in HFpEF as well as HFmrEF. It is assumed that the patients in both study arms will be treated optimally: subject to a guideline-compliant patient-individual treatment of heart failure and underlying diseases or risk factors such as hypertension, arrhythmias, kidney disease, dyslipoproteinaemia or diabetes mellitus as well as the concomitant symptoms, such as oedema. The adequate treatment of the underlying disease should be clearly documented in the dossier on the basis of the patient characteristics (e.g. HbA1c value, oedema, cardiac arrhythmias, etc.). The marketing authorisations and product information of the medicinal products are to be observed; deviations are to be justified separately.

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

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

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

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

2.1.3 Extent and probability of the additional benefit

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

Adults with symptomatic chronic heart failure with preserved ejection fraction HFpEF (LVEF > 50%) and with mildly reduced ejection fraction HFmrEF (LVEF > 40 to 49%)

Hint for a minor additional benefit

Justification:

The double-blind, placebo-controlled, randomised DELIVER study is available to assess the additional benefit of dapagliflozin. The DELIVER study enrolled adults with symptomatic NYHA class II to IV chronic heart failure with LVEF > 40%. As a prerequisite for enrolment in the study, participants had to have increased NT-proBNP[6] values, defined according to inclusion criteria as follows:

- NT-proBNP ≥ 300 pg/ml, if neither atrial fibrillation nor atrial flutter was present
- NT-proBNP ≥ 600 pg/ml in the presence of lasting atrial fibrillation or atrial flutter.

As a further inclusion criterion, patients had to have been diagnosed with structural heart disease (enlargement of the left atrium and/or left ventricular hypertrophy).

A total of 6,263 study participants were examined and randomised in a 1:1 ratio to the two study arms, dapagliflozin versus placebo, and stratified according to the criterion of a type 2 diabetes mellitus diagnosis. One third of the adults in the study had an LVEF < 50%, two thirds had an LVEF ≥ 50%. At the time of enrolment in the study, 45% of the participants had type 2 diabetes mellitus and about half had chronic kidney disease (CKD), defined as eGFR < 60 ml/min/1.73 m².

The treatment with dapagliflozin was carried out according to the recommendations in the product information. In the study, in addition to the study medication, a medicinal background therapy was administered for the treatment of heart failure as well as the respective underlying diseases, which according to the study protocol should be carried out according to the best standard in accordance with local guidelines and recommendations.

The DELIVER study was event-controlled, with a median treatment duration of about 2.4 years. Patient-relevant results were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Uncertainty of the study population

Due to the above-mentioned inclusion criteria regarding increased NT-proBNP values, eligible study participants, who had already passed the screening phase, were selected. This led to a limitation of the study population. Accordingly, 32% of the screened patients were excluded from enrolment in the study due to the required increased NT-proBNP values, although the approved therapeutic indication does not include any limitations with regard to NT-proBNP values, so that dapagliflozin would also have been indicated for this sub-population. The DELIVER study focused on adults with chronic heart failure and LVEF > 40% who had increased NT-proBNP values. This indicates a patient selection with relevant prognostic factors for an unfavourable course of chronic heart failure.

[6] NT-proBNP: N-terminal pro-B-type natriuretic peptide

Implementation of the appropriate comparator therapy

According to the guidelines, adequate treatment of relevant comorbidities - such as hypertension, arrhythmias, coronary artery heart disease, type 2 diabetes mellitus, chronic kidney disease and dyslipoproteinaemia – as well as concomitant symptoms should be ensured, especially in patients with HFpEF. In the presence of HFmrEF, the guidelines recommend treatment according to heart failure with reduced ejection fraction.

The study population is heterogeneous in terms of underlying diseases. The medicinal therapy of the underlying diseases carried out as background therapy is of particular importance in the assessment of the implementation of the appropriate comparator therapy.

At the start of the study, the vast majority of patients were receiving anti-hypertensive drugs. Thus, in about 72% of them, treatment with ACE inhibitors or ARBs was administered; in about 83% or 89%, beta receptor blockers or diuretics were used respectively. Treatment with MRA was given to about 42%, and with diuretics or ARNI[7], about 89% and 4% of patients were treated, respectively, at the start of the study.

In principle, adjustments to the therapy were possible in the course of the study. With the exception of the study medication for the intervention arm, the use of SGLT-2 inhibitors was excluded from the study. However, in exceptional cases, the use of SGLT-2 inhibitors was possible at the discretion of the principal investigator, provided that all other treatment options were considered and clinical use was indicated. In this case, the study medication had to be temporarily interrupted or discontinued. Overall, about 2% in the intervention or comparator arm received an SGLT-2 inhibitor during the study, of which a few patients received an SGLT-2 inhibitor in addition to the study medication.

With the exception of SGLT-2 inhibitors, there were no restrictions on concomitant medicinal treatments. Adjustments during the study due to newly started or changed therapies with an ACE inhibitor or ARB occurred in 15% in the intervention arm versus 20% in the comparator arm, while for MRA this was the case in 12% in the intervention arm versus approximately 17% in the comparator arm. Adjustment of therapy with diuretics was experienced by 27% of participants in the intervention arm versus 39% in the comparator arm, and with ARNI by approximately 3% in the intervention arm versus 4% in the comparator arm.

With regard to the concomitant anti-diabetic treatment during the study, it is noted that almost 40% of the study participants were already receiving medicinal anti-diabetic therapy at the start of the study. The mean HbA1c value in the patients with diabetes at the start of the study was 6.6%. Data on adjustments of antidiabetic therapies during the course of the study are only available for the product classes of SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors. According to this, a newly started antidiabetic therapy with SGLT-2 inhibitors, GLP-1 receptor agonists or DPP-4 inhibitors in the intervention or comparator arm respectively took place in about 2% of the study participants.

Overall, the concomitant medicinal therapies administered in the study indicate that comorbidities were largely adequately treated in the subjects studied.

With regard to the blood pressure values, it is noted that in 22% of the study participants the systolic blood pressure was inadequately adjusted with measured values of ≥ 140 mmHg at the start of the study. In the further course of the study, this value changed only slightly. In particular, uncertainties remain as to the extent to which the study participants in the comparator arm were able to achieve an optimum blood pressure setting during the course of the study, also with regard to the concomitant antidiuretic treatment.

[7] ARNI: Angiotensin receptor neprilysin inhibitor consisting of the fixed combination with sacubitril and valsartan

In addition, there is a lack of information on lipid parameters at the start of the study and in the further course of the study, so that overall it cannot be conclusively assessed to what extent the treatment of dyslipidaemia in the patients was carried out appropriately.

In view of the fact that there was a very high risk of the occurrence of cardiovascular events due to the manifest heart failure disease, and that adequate hypertension treatment and, in patients with type 2 diabetes mellitus, therapy with SGLT-2 inhibitors or GLP-1 receptor agonists would therefore have been indicated according to the guideline recommendations, the implementation of the appropriate comparator therapy in the study is fraught with uncertainty. Despite these uncertainties, a sufficient approximation to the appropriate comparator therapy is assumed overall, so that the present study can be used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall mortality and cardiovascular death presented additionally

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

Morbidity

Hospitalisation due to heart failure

Patients in the present therapeutic indication are usually hospitalised for heart failure in case of deterioration of their symptomatology because of their heart failure disease. Therefore, hospitalisation due to heart failure in the present case can be considered as approximating the clinical condition of symptom deterioration. Thus, the endpoint "hospitalisation due to heart failure" gives conclusions about the disease-specific morbidity and is used in this specific case.

For the endpoint *"hospitalisation due to heart failure"* for the time to first event, there is a statistically significant difference to the advantage of dapagliflozin compared to the comparator arm. For the early benefit assessment, operationalisation over time to first event is leading. For the additionally presented operationalisation "including repeat events", there was also a statistically significant difference to the advantage of dapagliflozin compared to the comparator arm.

Total hospitalisation

The endpoint "total hospitalisation" was collected as the time to the first occurrence of hospitalisation of any cause and the occurrence of hospitalisations of any cause (first and repeat). For the early benefit assessment, operationalisation over time to first event is leading.

The endpoint "total hospitalisation" for the time to first event shows no statistically significant difference between dapagliflozin versus the comparator arm.

Myocardial infarction and stroke

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

Renal morbidity

The endpoint "renal morbidity" is available for the following operationalisations:

- Confirmed sustained reduction of eGFR[8] by ≥ 50%
- Doubling of serum creatinine level accompanied by eGFR < 45 ml/min/ 1.73 m²

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.

Doubling of serum creatinine level accompanied by eGFR < 45 ml/min/ 1.73 m²

In half of the study participants in the DELIVER study, the eGFR was ≥ 60 ml/ min/ 1.73 m². The patient relevance of this endpoint with such high baseline eGFR values cannot be conclusively assessed. Furthermore, the operationalisation of the endpoint with the inclusion of serum creatinine values at the start of the study is considered unsuitable for showing a noticeable deterioration of their kidney function with sufficient certainty for all patients affected in the DELIVER study.

The endpoint of renal morbidity is therefore only presented additionally. Overall, for this endpoint, there were no statistically significant differences between the treatment arms.

Health status

EQ-5D VAS

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

PGIS

There is no information available regarding the assignment of severity for the endpoint of health status assessed by means of PGIS, which allows a classification as serious or severe. Therefore, this endpoint is assigned to the endpoint category of non-serious, non-severe symptoms or secondary complications.

For the endpoint of health status assessed by PGIS, there was a statistically significant difference in favour of dapagliflozin compared to the comparator arm. However, this difference is estimated to be no more than minor.

<u>Quality of life</u>

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

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

[8] eGFR: Estimated glomerular filtration rate

For the KCCQ-OSS clinical summary score, operationalised as an improvement of ≥ 15%, there was a statistically significant difference to the advantage of dapagliflozin compared with the comparator arm.

Side effects

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

Overall rates

Serious adverse events (SAEs) and discontinuation due to adverse events (AEs)

There were no statistically significant differences between the treatment arms for the endpoint SAE and discontinuation due to AEs.

Specific AEs

Urinary tract infection (AE) and genital infection (AE)

No suitable data are available for the endpoints of urinary tract infection (UTI) and genital infection (GE), as non-serious AEs were not systematically recorded in the study and it is known that the majority of these events belong to the category of non-serious side effects.

Diabetic ketoacidosis

For the endpoint of diabetic ketoacidosis, no statistically significant difference was detected between the treatment groups.

Gastrointestinal disorders (SAE)

In detail, there was a statistically significant difference in favour of dapagliflozin compared to the control arm in the specific SAE of gastrointestinal disorders.

COVID-19 (SAE)

In detail, the specific SAE of COVID-19 showed a statistically significant difference to the disadvantage of dapagliflozin compared to the control arm.

Overall assessment

The pharmaceutical company presents the placebo-controlled, double-blind, randomised DELIVER study for the early benefit assessment of dapagliflozin for the new therapeutic indication for the treatment of adults with symptomatic chronic heart failure with preserved ejection fraction (HFpEF) as well as mildly reduced ejection fraction (HFmrEF). NYHA class II to IV chronic heart failure patients with an LVEF[9] value ≥ 40% were studied, who also had to have increased NT-proBNP values (up to ≥ 300 pg/ ml or ≥ 600 pg/ ml for AF[10]). One third of the adults in the study had an LVEF < 50%, two thirds had an LVEF ≥ 50%. There was no statistically significant and relevant effect modification for the characteristic LVEF < 50% versus LVEF ≥ 50% at the start of the study.

The study medication dapagliflozin or placebo was administered in addition to medicinal background therapy for the treatment of heart failure and other underlying diseases, which

[9] LVEF: left ventricular ejection fraction
[10] AF: atrial fibrillation or atrial flutter

according to the study protocol should be according to the best standard according to local guidelines.

The median treatment duration of the study was about 2.4 years.

The therapy carried out in the study in the comparator arm largely corresponds to an optimised standard therapy for the treatment of heart failure as well as the underlying diseases, which was determined as the appropriate comparator therapy for the present therapeutic indication. Despite existing uncertainties, a sufficient approximation to the appropriate comparator therapy is assumed overall, so that the present study can be used to assess the total population.

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

In the morbidity category, a statistically significant advantage of dapagliflozin over the comparator arm is observed for the endpoint "hospitalisation due to heart failure". There were no statistically significant differences for the endpoint of total hospitalisation.

There are no statistically significant differences between the treatment arms for the other combined endpoints of the categories of morbidity, "myocardial infarction", each in the individual components of fatal and non-fatal myocardial infarction, and "stroke", also each in the individual components of fatal and non-fatal stroke.

For the endpoint of health status, assessed by EQ-5D VAS, there are no statistically significant differences. For the same endpoint assessed by PGIS, there is a statistically significant difference in favour of dapagliflozin, which, however, is no longer considered minor.

In the category of health-related quality of life, data are available for the clinical sum score KCCQ-OSS. For the operationalisation as an improvement of ≥ 15%, there are statistically significant differences to the advantage of dapagliflozin.

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

In the overall assessment of the results based on the positive effects of dapagliflozin in the avoidance of hospitalisation due to heart failure and in the improvement of ≥ 15% for the clinical sum score KCCQ-OSS in the category of health-related quality of life, a minor additional benefit of dapagliflozin compared to the appropriate comparator therapy is derived overall.

Reliability of data (probability of additional benefit)

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

There are uncertainties regarding the study population due to the inclusion criterion related to increased NT-proBNP levels as a requirement for enrolment in the study. 32% of the screened study participants were excluded because of too low NT-proBNP values, although the approved therapeutic indication does not provide any limitations with regard to NT-proBNP values.

Furthermore, the study medication, dapagliflozin versus placebo, should be administered in addition to medicinal background therapy for the treatment of heart failure as well as other underlying diseases, which according to the study protocol should be administered according to the best standard according to guidelines.

In the present therapeutic indication, special importance is attached to the treatment of comorbidities. Already at the start of the study, 22% of the patients had inadequately

controlled blood pressure. It is unclear to what extent optimum blood pressure control could be achieved in these subjects during the course of the study, especially in the comparator arm.

With regard to the anti-diabetic treatment during the study, it is noted that due to the exclusion of SGLT-2 inhibitors in the comparator arm and the low use of GLP-1 receptor agonists with < 5%, the guideline-compliant therapy of type 2 diabetes mellitus during the study is also subject to uncertainties. Overall, in the implementation of the appropriate comparator therapy in the study, a sufficient approximation to the appropriate comparator therapy is assumed.

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

2.1.4 Summary of the assessment

The present assessment is the early benefit assessment of the new therapeutic indication for the active ingredient dapagliflozin "for the treatment of adults with symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) > 40%".

For the patient population to be considered here – adults with symptomatic chronic heart failure with preserved ejection fraction HFpEF (LVEF > 50%) and with mildly reduced ejection fraction HFmrEF (LVEF > 40 to 49%) - the G-BA determined an optimised standard therapy for the treatment of symptomatic chronic heart failure with preserved ejection fraction or mildly reduced ejection fraction and the underlying diseases such as hypertension, arrhythmias, coronary artery heart disease, diabetes mellitus, chronic kidney disease, dyslipoproteinaemia as well as the concomitant symptoms as the appropriate comparator therapy.

The double-blind, randomised DELIVER study was presented. The administration of dapagliflozin versus placebo was investigated, each in addition to standard therapy of heart failure in NYHA class II to IV chronic heart failure patients with reduced LVEF > 40% and increased NT-proBNP values.

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

In the morbidity category for hospitalisation due to heart failure, there was a statically significant difference in each case to the advantage of dapagliflozin over the control arm. There were no statistically significant differences in total hospitalisation and the cardiovascular morbidity endpoints of myocardial infarction and stroke.

In the health-related quality of life category, there is a statistically significant difference to the advantage of dapagliflozin.

In the category of side effects, there were no statistically significant differences for the overall rates of SAEs and for discontinuation due to AEs.

There is uncertainty in the selection of patients with increased NT-proBNP levels. Overall, the implementation of the appropriate comparator therapy is assumed to be sufficiently close to the appropriate comparator therapy, although uncertainties remain in this regard as well. Therefore, the reliability of data is classified in the category "hint".

In the overall assessment of the results based on the positive effects in the avoidance of hospitalisation due to heart failure and in health-related quality of life, taking into account the uncertainties mentioned, a hint for a minor additional benefit of dapagliflozin is derived overall.

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.

For the determination of patient numbers, the G-BA takes into account the underlying data in the previous resolution in the present therapeutic indication of chronic heart failure with reduced ejection fraction LVEF > 40%[11].

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 July 2023):

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 August 2023).

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

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs. The recommended dose of empagliflozin is 10 mg 1 x daily.

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

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

[11] Resolution on empagliflozin dated 15 September 2022 https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/810/

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

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
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					
Optimised standard therapy	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Dapagliflozin	98 FCT	€ 239.26	€ 2.00	€ 0.00	€ 237.26
+ optimised standard therapy	Different from patient to patient				
Appropriate comparator therapy					
Optimised standard therapy	Different from patient to patient				
Abbreviation: FCT = film-coated tablets					

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Costs for additionally required SHI services:

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

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

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

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

medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

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

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

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

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

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 25 June 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The appropriate comparator therapy was adjusted on 4 January 2023.

On 17 February 2023, 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, sentence 2 VerfO.

By letter dated 27 February 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the 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 30 May 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 June 2023. The deadline for submitting written statements was 22 June 2023.

The oral hearing was held on 10 July 2023.

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

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 8 August 2023, and the proposed resolution was approved.

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 June 2019	Determination of the appropriate comparator therapy
Working group Section 35a	4 January 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	4 July 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 July 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 July 2023 1 August 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	8 August 2023	Concluding discussion of the draft resolution
Plenum	17 August 2023	Adoption of the resolution on the amendment of Annex XII and Annex XIIa Pharmaceuticals Directive

Berlin, 17 August 2023

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

Prof. Hecken