Gemeinsamer Bundesausschuss

Justification

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Dapagliflozin (new therapeutic indication: chronic heart failure)

of 20 May 2021

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:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th 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 May 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 3 December 2020, 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 December 2008, p. 7).

On 30 November 2020, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company on the approval of a new area of application, the pharmaceutical company has submitted a dossier 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 (VerfO) of the G-BA on the active ingredient dapagliflozin with the new therapeutic indication (chronic heart failure). The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 March 2021 on the G-BA website at (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. 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 new indication of dapagliflozin (Forxiga) according to the SmPC

"In heart failure, Forxiga is used in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction."

Therapeutic indication of the resolution (resolution from the 20/05/2021):

see new therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with symptomatic, chronic heart failure with reduced ejection fraction

Appropriate comparator therapy:

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

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

1 General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 Federal Joint Committee 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 classes are generally approved for the treatment of heart failure:
- Angiotensin-converting enzyme inhibitors (ACE inhibitors): Captopril, cilazapril, enalapril, lisinopril, perindopril and ramipril
- AT1 receptor blockers (ARBs): candesartan, losartan and valsartan
- Beta blockers: bisoprolol, carvedilol, metoprolol succinate and nebivolol
- Digitalis glycosides
- Diuretics: e.g. thiazides (hydrochlorothiazide)
- Aldosterone antagonists (MRA): e.g. spironolactone, eplerenone
- Ivabradine
- Sacubitril/Valsartan

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

on 2. Non-medicinal treatments are not considered for the therapeutic indication.

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

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

- There are requirements for structured treatment programmes for patients with chronic heart failure (https://www.g-ba.de/downloads/62-492-2416/DMP-A-RL_2020-11-20_iK-2021-02-25.pdf).

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

- Sacubitril/Valsartan (Resolution of 16 June 2016)

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.

It is assumed that dapagliflozin is used in addition to standard therapy for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

The guidelines recommend both ACE inhibitors and beta blockers for patients with heart failure in all NYHA classes. AT1 receptor blockers (ARBs) are recommended for ACE inhibitor intolerance according to their approval. According to guidelines, the use of diuretics in NYHA class II - additive to standard therapy - is only recommended if signs of fluid retention are also present. Aldosterone antagonists (mineral corticoid receptor antagonist, MRA) are recommended in NYHA class II-IV patients who remain symptomatic despite therapy with an ACE inhibitor and beta-blocker and in NYHA class II patients after myocardial infarction. Due to their limited safety profile, digitalis glycosides are mainly recommended in the second-line setting, in case of inadequate response to standard therapy. This class of active substances is therefore also not regularly considered as an appropriate comparator therapy in the present indication. The same is true for ivabradine, as it is recommended only in beta-blocker intolerance or only additively in patients with heart rates ≥ 75/min. According to guideline recommendations[2] patients who are symptomatic despite guideline-targeted therapy with ACE inhibitors, beta blockers, and MRA should be recommended to switch from ACE inhibitors to sacubitril/valsartan. However, due to the current uncertainties with sacubitril/valsartan regarding difficulties in the conversion phase and the side effect profile, special attention should be paid to contraindications and intolerances in these patients.

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

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

Adjustment of the baseline/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 therapy changes or therapy initiation for the treatment of new

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

symptoms as well as for the worsening of existing symptoms. The concomitant and basic medication at study entry 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 order.

2.1.3 Extent and probability of the additional benefit

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

There is evidence of substantial additional benefit for dapagliflozin for the treatment of symptomatic chronic heart failure with reduced ejection fraction in adults.

Justification:

For the benefit assessment of dapagliflozin, the placebo-controlled, double-blind, randomised study DAPA-HF is available. A total of 4744 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 heart failure therapy for at least 4 weeks before study inclusion were included. This standard therapy should include, unless contraindicated, ACE inhibitors, ARB[3] or sacubitril/valsartan in combination with a beta blocker and, if appropriate, an MRA[4].

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.

Patient characteristics are also comparable between treatment arms: On average, the patients in the DAPA-HF study were 66 years old, mostly male (77%) and predominantly of European origin. 42% of the patients were diagnosed with diabetes mellitus type 2 at the time of inclusion in the study. A majority of patients had mild performance limitations due to their

3 ARB: Angiotensin II receptor blocker
4 MRA: Mineralocorticoid receptor antagonist

disease (NYHA class II), about 32% had severe performance limitations (NYHA class III), and about 1% also had limitations at rest (NYHA class IV). On average, patients had an LVEF of 31%.

Overall, the cross-endpoint bias potential for the DAPA-HF study is rated as low.

Implementation of the appropriate comparator therapy

An optimised standard therapy for the treatment of symptomatic, chronic heart failure and the underlying diseases, such as hypertonia, cardiac arrhythmias, coronary heart disease, diabetes mellitus, hypercholesterolaemia, as well as the accompanying symptoms, was determined as the appropriate comparator therapy. Overall, the adequate implementation of the appropriate comparator therapy in the DAPA-HF study is subject to uncertainties, which are described below.

In the study, patients were to receive patient-specific therapy according to locally accepted guidelines for the treatment of both heart failure and other cardiovascular risk factors and comorbidities. 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.

In the study, 83% of patients received treatment with ACE inhibitors or ARBs, approximately 96% received beta blockers, and approximately 71% received additional MRAs, with approximately half of patients receiving an adjustment in heart failure therapy during the course of the study: Forty-seven percent of patients in the dapagliflozin arm and 50% in the control arm received a dose increase or reinitiation of therapy, but no detailed information is available on the nature of the adjustments, such as which specific drug changes were made or in how many patients dose adjustments were made for individual active ingredients. Although the pharmaceutical company's dossier outlines reasons for not treating or not reaching the target dose recommended in the guideline for each active ingredient, for example, almost 30% of patients in the study did not receive MRAs, and for half of these patients the reasons for not receiving treatment remain unclear.
Overall, it thus remains unclear whether the patients in the DAPA-HF study would have benefitted from further adjustments to their therapy to ensure optimal treatment.

Furthermore, according to the National Health Care Guideline[5], a switch to sacubitril/valsartan (angiotensin receptor neprilysin inhibitor, ARNI) should be recommended to patients who show symptoms despite guideline-compliant therapy with ACE inhibitors or ARBs, beta blockers and MRAs. However, in view of the current uncertainties regarding the side effect profile of sacubitril/valsartan and the resulting difficulties, particularly in the transition phase from prior therapy with an ACE inhibitor or ARB to sacubitril/valsartan, special attention should be paid to contraindications and intolerances in these patients. Prior to inclusion in the DAPA-HF study, approximately 11% of patients received sacubitril/valsartan; over the course of the study, approximately 16% were treated with sacubitril/valsartan. According to the pharmaceutical company's dossier, the main reason given for not being treated with ARNI is treatment with ACE inhibitors (approx. 53%) or with ARBs (approx. 25%). In the course of the written statement procedure, the medical societies argued that the combination of sacubitril and valsartan is not suitable for all patients, even if they still show symptoms, due to its side effect profile and the close monitoring that is

5 National Health Care Guideline on Chronic Heart Failure (3rd edition, 2019, version 2): https://www.leitlinien.de/nvl/herzinsuffizienz

therefore required, particularly during the conversion phase. In the view of the professional societies, the DAPA-HF study would reflect the reality of care with regard to the use of sacubitril/valsartan.
However, uncertainties remain as to whether additional patients in the DAPA-HF study who were symptomatic despite guideline-guided therapy with ACE inhibitors or ARBs, beta-blockers, and MRAs could have received a change in therapy to sacubitril/valsartan.

Taken together, despite the uncertainties described, it is assumed that a sufficient approximation to the appropriate comparator therapy was achieved in the DAPA-HF study.

Extent and probability of the additional benefit

Mortality

All-cause mortality

In the DAPA-HF study, statistically significantly fewer patients died in the dapagliflozin arm compared to the control arm (11.6% vs 13.9%). There was an effect modification with regard to the severity of heart failure according to NYHA class: patients with NYHA class II had statistically significantly fewer deaths in the dapagliflozin arm (7.8% vs 12.0%). In contrast, in patients with NYHA class III/IV, more deaths occurred in the dapagliflozin arm compared with the control arm (19.7% vs 17.7%), but there was no statistically significant difference between the treatment groups.

Cardiovascular mortality

Regarding the supplemental cardiovascular mortality, statistically significantly fewer deaths occurred in the dapagliflozin arm compared to the control arm (9.6% vs 11.5%). There was also an effect modification with regard to the severity of heart failure according to NYHA class: patients with NYHA class II had statistically significantly fewer deaths in the dapagliflozin arm, and patients with NYHA class III/IV had no statistically significant difference between the treatment groups.

Morbidity

combined endpoint on cardiovascular morbidity

The primary composite endpoint for cardiovascular morbidity includes the individual components of cardiovascular mortality, hospitalisation for heart failure, and emergency department visits for heart failure. This operationalisation represents cardiovascular morbidity only to a limited extent, since relevant cardiovascular endpoints such as nonfatal myocardial infarctions and strokes are not included. Accordingly, the primary composite endpoint is not used for the benefit assessment.

Total hospitalisation

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

Myocardial Infarction

There was no statistically significant difference between the treatment groups for the combined endpoint of nonfatal and fatal myocardial infarctions or for the two individual components.

Stroke

For the combined endpoint of strokes (nonfatal and fatal strokes), as well as for the two individual components, there was no statistically significant difference between the treatment groups.

Renal morbidity

Renal morbidity was assessed by a composite endpoint consisting of the single endpoints sustained eGFR[6]decrease of 50%, end-stage renal disease (ESRD) and renal death. Overall, few events occurred in the study arms, and there was no statistically significant difference between the treatment groups for either the combined endpoint or the individual components.

health status

EQ-5D VAS (visual analogue scale of the European Quality of Life Questionnaire - 5 Dimensions)

For the assessment of the general health status, the results of the EQ-5D VAS instrument are available on a scale of 1 to 100. Higher values indicate a better health status. There is a statistically significant difference between the treatment arms for the benefit of dapagliflozin compared with the control arm, but the 95% confidence interval of the standardised mean difference (Hedges' g) is not completely outside the irrelevance range of -0.2 to 0.2, and it cannot be inferred that the observed effect is relevant.

PGIC (Patient Global Impression of Change) and PGIS (Patient Global Impression of Severity)

In the PGIC[7] patients provide a self-assessment of the improvement or worsening of their symptoms on a seven-point scale from "much better" to "much worse" and in the PGIS[8] on the severity of their symptoms using a six-point scale from 1 (no symptoms) to 6 (very severe symptoms).

With regard to PGIC, 93.5% of patients in the dapagliflozin arm and 92.9% in the control arm showed no worsening in PGIC, thus there is no statistically significant difference between the treatment arms.

In PGIS, 78.0% of patients in the dapagliflozin arm and 74.9% in the control arm had no worsening in PGIS. There are no statistically significant differences between the treatment arms.

Interim summary of morbidity

With regard to morbidity, the DAPA-HF study showed statistically significant positive results for the endpoint "total hospitalisation" in favour of dapagliflozin. With regard to health status (EQ-5D VAS as well as PGIS), there are statistically significant advantages with dapagliflozin, but no clinically relevant differences can be derived with the EQ-5D VAS. In the PGIC no statistically significant difference was detected between the treatment arms. Thus, the results for the health status endpoint are inconsistent. A benefit for dapagliflozin is not inferred for this endpoint.

6 eGFR: estimated glomerular filtration rate.
7 PGIC: Overall, how would you rate the change in your heart failure symptoms since starting this study? Much better/Moderately better/A little better/About the same/A little worse/Moderately worse/Much worse
8 PGIS: Overall, how would you rate the severity of your heart failure symptoms today? No symptoms/Very mild/Mild/Moderate/Severe/Very Severe

However, in the other morbidity endpoints, there were no statistically significant differences between the treatment arms for either endpoint.

Quality of life

Kansas City Cardiomyopathy Questionnaire (KCCQ)

For the endpoint category health-related quality of life, the results of the questionnaire KCCQ are available.
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 pharmaceutical company presents in the dossier both the results on mean differences and responder analyses (improvement or worsening by 5 points) of the KCCQ-OSS (Overall Summary Score), consisting of the domains physical limitations, symptoms, social impairment and quality of life, and the KCCQ symptom score. For the remaining 3 valid domains of the KCCQ (physical limitation, social limitation and psychological quality of life), the pharmaceutical company does not submit responder analyses.

According to IQWiG's current methodological approach (Methods 6.0, published on 5.11.2020), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for *post hoc* analyses of exactly 15% of the scale range) to be necessary for patient-reported endpoints in order to represent a noticeable change with sufficient certainty.

In the written statement, the pharmaceutical company presents responder analyses with an improvement of 15 points (corresponding to 15% of the scale range). For both the 5 and 15 point improvement responder analyses, there were statistically significant differences between treatment arms for the benefit of dapagliflozin compared to control.

Side effects

In the DAPA-HF study, there was no systematic collection of adverse events (AEs) regardless of severity. Only non-serious AEs that led to treatment 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)

In the DAPA-HF study, statistically significantly fewer SAEs occurred in the dapagliflozin arm compared to the control arm (27.8% vs 30.7%).

Discontinuation because of AEs

In the study, 111 (4.7%) patients in the dapagliflozin arm and 116 (4.9%) in the control arm discontinued therapy due to AEs. There are no statistically significant differences between the treatment groups.

Specific AEs

Urinary tract infection, diseases of the genitals and mammary gland, diabetic ketoacidosis

In detail, the specific UE urinary tract infection (PT[9]) and diseases of the genital organs and mammary gland (SOC[10]) occurred in only a few patients each (≤ 2.0%). Diabetic ketoacidosis (PT) occurred in only 3 (0.1%) patients in the dapagliflozin arm. However, there were no statistically significant differences between the treatment arms for either endpoint.

Respiratory, thoracic and mediastinal disorders

For SOC Respiratory, thoracic and mediastinal disorders, it cannot be ruled out that events potentially attributable to the symptomatology of the underlying condition (e.g. dyspnoea) are also included. In the DAPA-HF studies, 57 (2.4%) patients in the dapagliflozin arm and 88 (3.7%) in the control arm experienced respiratory, thoracic and mediastinal disease. The results are statistically significantly different in favour of dapagliflozin.

Interim conclusion on side effects

For the endpoint adverse events, it should be noted that in the DAPA-HF study there was no systematic ascertainment of AEs independent of severity. Only non-serious AEs that led to treatment discontinuation or dose adjustment or belonged to a selection of AEs predefined by the pharmaceutical company were recorded.

In the DAPA-HF study, there are statistically significant positive results for the endpoint "SAE" and in detail for the specific AE "diseases of the respiratory tract, chest and mediastinum (SOC)" in favour of dapagliflozin. However, in the other morbidity endpoints, there were no statistically significant differences between the treatment arms for either endpoint.

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 heart failure therapy) over approximately 18 months in patients with symptomatic heart failure of NYHA class II to IV with reduced ejection fraction.

For the endpoint category mortality, both for the endpoint "all-cause mortality" and for the additionally presented "cardiovascular mortality", a statistically significant advantage was shown for dapagliflozin compared to the control. For both endpoints, there was an effect modification with regard to the severity of heart failure according to NYHA class: patients with NYHA class II experienced statistically significantly fewer deaths with dapagliflozin. In patients with NYHA class III/IV, there were no statistically significant differences between treatment groups.

With regard to morbidity, the DAPA-HF study showed statistically significant positive results for the endpoint "total hospitalisation" in favour of dapagliflozin. With regard to health status (EQ-5D VAS as well as PGIS), there are statistically significant advantages with dapagliflozin, but no clinically relevant differences can be derived for the EQ-5D VAS. For the PGIC, there is no statistically significant difference between the two treatment arms. Thus, the results for the health status endpoint are inconsistent. A benefit for dapagliflozin is not inferred for this

9PT: preferred term
10 SOC: System Organ Class

endpoint. However, in the other morbidity endpoints, there were no statistically significant differences between the treatment arms for either endpoint.

With regard to disease-specific quality of life (KCCQ-OSS), there were statistically significant differences between the treatment arms in favour of dapagliflozin in both the responder analyses with an improvement of 5 and 15 points.

For the endpoint adverse events, it should be noted that in the DAPA-HF study there was no systematic ascertainment of AEs independent of severity. Only non-serious AEs that led to treatment discontinuation or dose adjustment or belonged to a selection of AEs predefined by the pharmaceutical company were recorded. Overall, the DAPA-HF study showed statistically significant positive results in favour of dapagliflozin for the endpoint "SAE" and in detail for the specific AE "respiratory, thoracic and mediastinal disorders (SOC)". However, in the other morbidity endpoints, there were no statistically significant differences between the treatment arms for either endpoint.

In the overall results of the DAPA-HF study, there were statistically significant positive effects for dapagliflozin in all endpoint categories: Mortality (all-cause mortality and cardiovascular mortality, but only in patients with NYHA class II), morbidity (total hospitalisation), health-related quality of life (using the KCCQ-OSS) and adverse events (SAEs and in detail for a specific AE). With regard to the results of all-cause mortality and also cardiovascular mortality, it should be noted that only patients with NYHA class II, i.e. with mild limitations in physical performance, showed a benefit with dapagliflozin. There was no mortality benefit in patients with NYHA class III/IV. Although the NYHA classification is a well-established classification of patients with regard to the severity of heart failure, the distinction between the stages is sometimes blurred and may also differ from patient to patient. In particular, a clear distinction between NYHA class II (complaints during *everyday* physical exertion) and NYHA class III (complaints during *low* physical exertion) does not appear possible in order to differentiate between different patient populations for the benefit assessment. Nevertheless, the results of the DAPA-HF study suggest that patients with more severe heart failure do not benefit from dapagliflozin in terms of mortality.
The G-BA classifies the extent of the additional benefit of dapagliflozin in the present indication due to the limited data on the basis of the criteria in Section 5, paragraph 7, of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as considerable taking into account the severity of the disease and the therapeutic objective in the treatment of the disease.

Reliability of data (probability of additional benefit)

The study has uncertainties that limit the significance of the results

Based on the effect modification by the characteristic NYHA classification for all-cause mortality and also for the supplementary cardiovascular mortality, it cannot be excluded that patients with more severe heart failure do not benefit from dapagliflozin with regard to mortality. Furthermore, the implementation of the appropriate comparative therapy is subject to uncertainties, which result in particular from the fact that although approximately half of all patients in the study received a dose increase or a new initiation of their therapy, no detailed information is available on the type of adjustments, such as which specific drug changes were made or in how many patients dose adjustments were made for individual active ingredients. Although the pharmaceutical company's dossier presents reasons for not treating or not reaching the target dose recommended in the guideline for the individual

active ingredients, overall it remains unclear whether the patients in the DAPA-HF study would have required further adjustments to their therapy to ensure optimal treatment of their heart failure. Despite the plausible explanations provided by the professional societies as to why the switch from an ACE inhibitor or ARB to sacubitril/valsartan recommended in the guidelines in the case of persisting symptoms encounters problems in the reality of care, uncertainties remain as to whether other patients in the DAPA-HF study who show symptoms despite guideline-compliant therapy with ACE inhibitors or ARBs, beta-blockers and MRAs could have received a change in therapy to sacubitril/valsartan.

Furthermore, due to the lack of a systematic survey of AE, side effects cannot be fully assessed regardless of severity. Data on non-serious AEs are missing, as only non-serious AEs were recorded that led to treatment 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 the statements is therefore classified as "hint".

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient dapagliflozin. The therapeutic indication evaluated here is "In heart failure, Forxiga is used in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction."

The G-BA determined the appropriate comparator therapy to be "an optimised standard therapy for the treatment of symptomatic, chronic heart failure and the underlying diseases, such as hypertension, cardiac arrhythmias, coronary heart disease, diabetes mellitus, hypercholesterolaemia and the accompanying symptoms".

The DAPA-HF study was available for the benefit assessment. It investigated dapagliflozin in comparison with placebo (in each case in addition to optimal standard therapy) in patients with symptomatic heart failure of NYHA class II to IV with reduced ejection fraction.

For both, all-cause and supplemental cardiovascular mortality, there is a statistically significant benefit in favour of dapagliflozin. In each case, there was an effect modification with regard to the severity of heart failure: patients with NYHA class II had statistically significantly fewer deaths with dapagliflozin; with NYHA class III/IV, there was no statistically significant difference between the treatment groups.

With regard to morbidity (total hospitalisation) and quality of life (KCCQ-OSS), there are statistically significant positive results in favour of dapagliflozin.

Among adverse events, there are statistically significant results in favour of dapagliflozin for SAEs and in detail for specific AEs. However, in the other morbidity endpoints and other side effects endpoints, there were no statistically significant differences between the treatment arms for either endpoint.

Overall, the study has uncertainties that limit the validity of the results. Due to effect modification with respect to the severity of heart failure on mortality, it is uncertain whether all patients in the therapeutic area benefit equally from treatment with dapagliflozin. Furthermore, it is unclear whether patients would have required further adjustments to their therapy to ensure optimal treatment of their heart failure. In addition, the study did not

systematically collect data on AE regardless of severity, so that side effects cannot be fully assessed.

In the overall view of the positive effects in all endpoint categories of the DAPA-HF study, taking into account the uncertainties mentioned above, the G-BA found a hint of a considerable additional benefit.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance.

The resolution is based on the information from the dossier of the pharmaceutical company. Overall, the patient number of approx. 2,061,700 to 2,273,000 patients derived by the pharmaceutical company is subject to uncertainties, but is considered to be a largely plausible order of magnitude.

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: 23 April 2021):
https://www.ema.europa.eu/documents/product-information/forxiga-epar-product-information_de.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 May 2021).

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 recommended dose of dapagliflozin is 10 mg once daily.

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

Since the optimised standard therapy of heart failure is patient-specific, no concrete costs for the appropriate comparative therapy can be named at present. In addition, optimised standard therapy for the treatment of symptomatic chronic heart failure 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 duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Dapagliflozin	1 x daily	365	1	365
+ optimised standard therapy	varies from patient to patient			
Appropriate comparator therapy				
optimised standard treatment	varies from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ 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	varies from patient to patient				
Appropriate comparator therapy					
optimised standard treatment	varies 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 Sections 130 and 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. 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 product:

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	€ 158.48	€ 1.77	€ 0.00	€ 156.71
+ optimised standard therapy	varies from patient to patient				
Appropriate comparator therapy					
optimised standard treatment	varies from patient to patient				
Abbreviations: FCT = Film-coated tablets					

LAUER-TAXE® last revised: 1 May 2021

Costs for additionally required SHI services:

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

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

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

3. Bureaucracy cost calculation

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 July 2016.

A review of the appropriate comparator therapy defined by the G-BA took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 May 2020.

On 30 November 2020, 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 1, sentence 2 VerfO.

By letter dated 30 November 2020 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 25 February 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2021. The deadline for submitting written statements was 22 March 2021.

The oral hearing was held on 06 April 2021.

By letter dated 7 April 2021, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 30 April 2021.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 11 May 2021, and the draft resolution was approved.

At its session on 20 May 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 July 2016	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	26 May 2020	Implementation of the appropriate comparator therapy
Working group Section 35a	31 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee	6 April 2021 7 April 2021	Conduct of the oral hearing,

Medicinal products		Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	14 April 2021 5 May 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	11 May 2021	Concluding consultation of the draft resolution
Plenum	20 May 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 May 2021

Federal Joint Committee in accordance with Section 91 SGB V The chairman

Prof. Hecken