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
Empagliflozin (new therapeutic indication: chronic heart failure)

of 6 January 2022

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 of the medical product 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient empagliflozin (Jardiance) was listed for the first time on 15 August 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 17 June 2021, empagliflozin 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, p. 7).

On 12 July 2021, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in 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 empagliflozin 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 the website of the G-BA (www.g-ba.de) on 15 October 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of empagliflozin 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, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by 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 empagliflozin.

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 Empagliflozin (Jardiance) in accordance with the product information

Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

Therapeutic indication of the resolution (resolution of 6 January 2022):

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 for empagliflozin:

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

[1] General Methods, version 6.0 from 05.11.2020. 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, in principle, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant advantage shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. The following active ingredients or active ingredients from the following product 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-adrenoceptor antagonists: bisoprolol, carvedilol, metoprolol succinate and nebivolol
- digitalis glycosides
- diuretics: e.g. thiazides (hydrochlorothiazide)
- mineralocorticoid receptor antagonists (MRAs): e.g. spironolactone, eplerenone
- ivabradine
- sacubitril/valsartan
- the SGLT-2 inhibitor dapagliflozin

The following limitations 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-adrenoceptor antagonists 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 oedemas are due to heart failure or, as with the active ingredient hydrochlorothiazide, as adjunctive symptomatic therapy for chronic heart failure in addition to ACE inhibitors.

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:

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/62-492-2574/DMP-A-RL_2021-03-18_iK-2021-10-01.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)
- Dapagliflozin (resolution of 20 May 2021)

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

The present study assumes that empagliflozin 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-adrenoceptor antagonists for patients with heart failure in all NYHA classes. AT1 receptor blockers (ARBs) are recommended for ACE inhibitor intolerance according to the marketing authorisation. 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. Mineralocorticoid receptor antagonists (MRAs) are recommended in NYHA class II-IV patients who remain symptomatic despite therapy with an ACE inhibitor and beta-adrenoceptor antagonists 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 product class is therefore also not regularly considered as an appropriate comparator therapy in the present therapeutic indication. The same is true for ivabradine, as it is recommended only in beta-adrenoceptor antagonists 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-adrenoceptor antagonists 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, an optimised standard therapy for the treatment of symptomatic chronic heart failure and underlying conditions, such as hypertension, arrhythmias, coronary artery disease, diabetes mellitus, hypercholesterolaemia, and concomitant symptoms is determined to be an appropriate comparator therapy for empagliflozin for the treatment of adults with symptomatic chronic heart failure with reduced ejection fraction.

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

Since the administration of empagliflozin is in addition to standard therapy, it is assumed that the patients in both study arms will be treated optimally: a guideline-compliant patient-individual 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 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 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.

2.1.3 Extent and probability of the additional benefit

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

Adults with symptomatic, chronic heart failure with reduced ejection fraction

Hint for a minor additional benefit

Justification:

For the assessment of the additional benefit of empagliflozin, the pharmaceutical company presents the placebo-controlled, double-blind, randomised EMPEROR-Reduced study, in which patients with chronic heart failure of NYHA classes II to IV and reduced left ventricular ejection fraction (LVEF) ≤ 40% were examined. For enrolment in the study, participants also had to have increased NT-proBNP[3] values at the first visit, defined according to inclusion criteria as follows:

- NT-proBNP ≥ 2,500 pg/ml (≥ 5,000 pg/ml with AF[4]), if LVEF 36% ≤ to ≤ 40%
- NT-proBNP ≥ 1,000 pg/ml (≥ 2,000 pg/ml with AF) if LVEF 31% ≤ to ≤ 35%:

[3] NT-proBNP: N-terminal pro B-type natriuretic peptide
[4] AF: atrial fibrillation or atrial flutter

- NT-proBNP ≥ 600 pg/ml (≥ 1,200 pg/ml with AF), if LVEF ≤ 30%, or if LVEF ≤ 40% and hospitalisation due to heart failure has been documented within the last 12 months.

The medicinal therapy administered for heart failure consisted of combinations of the product classes ACE inhibitors, ARB[5], beta-adrenoceptor antagonists, oral diuretics, MRA[6], sacubitril/valsartan and ivabradine, and should comply with national and international recommendations. If necessary, the provision of care with defibrillators (ICD[7]) and cardiac resynchronisation therapies (CRT) should also be ensured.

A total of 3,730 study participants were enrolled and randomised in a 1:1 ratio to the two study arms, empagliflozin versus placebo. Patient-relevant results were recorded in the categories of mortality, morbidity, health-related quality of life and side effects. The study was event-controlled, with a median treatment duration of 1.2 years.

The SUGAR-DM-HF and EMPA-TROPISM studies which were presented additionally by the pharmaceutical company are not used for the present benefit assessment.[8]

Limitation of the investigated study population

Due to the above-mentioned inclusion criteria regarding increased NT-ProBNP values, eligible patients with chronic heart failure and reduced ejection fraction, who had already passed the screening phase, were selected. This led to a limitation of the study population. Accordingly, 36% of the screened study participants 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 empagliflozin would also have been indicated for this sub-population. In the EMPEROR-Reduced study, patients with severely reduced LVEF and increased NT-proBNP values or who had already been hospitalised for heart failure were studied, in particular. This indicates a patient selection with relevant prognostic factors for an unfavourable course of chronic heart failure.

Implementation of the appropriate comparator therapy

In the study, an adequate, patient-individual therapy of both heart failure and other cardiovascular risk factors and comorbidities (in particular, type 2 diabetes mellitus) was to be guaranteed in accordance with national and international recommendations. During the study, adjustments could be made in the medicinal therapy for heart failure. However, therapy had to be stable for at least one week before the first visit and during the screening phase until randomisation.

In the EMPEROR-Reduced study, a total of 73% of patients received treatment with ACE inhibitors or ARBs, about 96% received beta-blockers and 77% also received MRA. With regard to the therapy adjustments made during the study, 32% of study participants in the intervention arm versus 39% in the comparator arm started or changed to a medicinal therapy for the treatment of heart failure. Here, the most frequent adjustment concerned treatment with diuretics. For example, at the start of study, about 30% of the patients had no therapy with MRA. In the further course of the study, 7% in the intervention arm and 9% in the comparator arm started or changed to a new therapy with MRA.

[5] ARB: AT1 receptor blocker
[6] Mineralocorticoid receptor antagonist
[7] ICD: implantable cardioverter / defibrillator
[8] The SUGAR-DM-HF and EMPA-TROPISM studies are described in IQWiG's dossier assessment (A21-93)

Detailed information on the type of therapy adjustments carried out as well as the therapies for the treatment of comorbidities and their adjustments are not available.

Furthermore, according to the National Health Care Guideline[2], a switch to sacubitril/valsartan (angiotensin receptor neprilysin inhibitor, ARNI) is recommended to patients who show symptoms despite guideline-compliant therapy with ACE inhibitors or ARBs, beta-blockers and MRAs. However, due to the current uncertainties regarding difficulties in the conversion phase and the side effect profile, special attention must be paid to contraindications and intolerances in these patients. With regard to the use of sacubitril/valsartan, it is noted that 19% of the patients were pretreated with sacubitril/valsartan at the start of study and 7% had their therapy adjusted or restarted with sacubitril/valsartan during the course of the study. It is assumed that the escalation with sacubitril/valsartan in the study largely corresponds to the reality of care in Germany.

Overall, at approx. 65%, a relatively high percentage of study participants who did not experience any therapy adjustment during the study can be assumed. In the comparison arm, far fewer than half of the study participants in the comparator arm received treatment adjustments. In view of the fact that mainly adults with relevant prognostic factors for an unfavourable course of chronic heart failure were examined due to the inclusion criteria, and less than 50% of the patients underwent a therapy adjustment in the course of the study, it cannot be conclusively assessed whether all optimisation options were actually exhausted in the study.

In the overall assessment, it cannot be clearly assessed whether all optimisation options as part of the appropriate comparator therapy, if further adjustment was indicated, were actually exhausted within the framework of the patient-individual therapy carried out in the study. Despite these uncertainties, a sufficient approximation to the appropriate comparator therapy is assumed.

Extent and probability of the additional benefit

Mortality

Overall mortality and cardiovascular death

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

Morbidity

Total hospitalisation

For the endpoint "total hospitalisation", the EMPEROR-Reduced study showed a statistically significant advantage of empagliflozin compared to the control arm.

Myocardial infarction

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

Stroke

For the combined endpoint "stroke", consisting of the individual components "non-fatal stroke" and "fatal stroke", there are no statistically significant differences between the treatment arms. There are also no statistically significant differences for the individual components.

Renal morbidity

The endpoint "renal morbidity" was collected as part of a combined endpoint. In addition, data were available in the dossier for the individual components "chronic dialysis", "kidney transplantation" and "sustained reduction in estimated glomerular filtration rate (eGFR)". The latter was operationalised as either a sustained eGFR reduction of ≥ 40% or sustained eGFR < 15 ml/min/1.73 m² *(if eGFR ≥ 30 ml/min/1.73 m² was present at the start of study)* or sustained eGFR < 10 ml/min/1.73 m² *(if eGFR < 30 ml/min/1.73 m² was present at the start of study)*.

The individual components "chronic dialysis", "kidney transplantation", and sustained eGFR < 15 ml/min/1.73 m² or < 10 ml/min/1.73 m² are patient-relevant and comparable in terms of severity. In contrast, a relative reduction in eGFR of ≥ 40% is not comparable to the other endpoints in terms of severity. For this reason, a summary of the three individual components is not meaningful and cannot be interpreted.

In the written statement procedure, data with a further operationalisation of the combined renal morbidity endpoint were defined as follows:

- sustained reduction of eGFR by ≥ 50%
- end-stage renal disease (ESRD) with operationalisation:
  - chronic dialysis,
  - kidney transplant, or
  - sustained eGFR < 15 ml/min/1.73 m²
- renal death.

In just over half of the participants in the EMPEROR-Reduced study, the eGFR was ≥ 60 ml/min/1.73 m². A relative "reduction of eGFR by ≥ 50%" with such high baseline values of eGFR is furthermore not comparable in terms of severity with the other individual components such as "end-stage kidney disease" or "renal death". A summary of all three individual components in a combined endpoint is therefore not meaningful and cannot be interpreted. The endpoint is therefore not used. In addition, the data submitted by the pharmaceutical company did not provide any information on statistical significance, no effect estimators and no Kaplan-Meier curves for the individual components.

In a recent resolution in the same therapeutic indication, this combined endpoint was also investigated in the assessed study. The results were not relevant to the assessment due to the lack of statistical significance, so the corresponding substantive discussion was not published.

Health status

Health status was assessed in the study using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the improvement of ≥ 15 points in week 52, there is a statistically significant difference to the advantage of empagliflozin compared to the comparator arm. However, this difference is no more than minor.

Quality of life

Kansas City Cardiomyopathy Questionnaire (KCCQ)

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.

According to IQWiG's current methodological approach (methods paper 6.0, published on 05.11.2021), 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.

For the clinical sum score KCCQ-OSS, operationalised as an improvement of ≥ 15%, there were no statistically significant differences between the treatment arms.

The pharmaceutical company submits evaluations of responder analyses using the criterion of improvement by ≥ 5 points. This results in a statistically significant difference to the advantage of empagliflozin compared to the comparator arm. These results are taken into account in the present case.

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 (SAE)

For the endpoint SAE, there is a statistically significant difference between the treatment groups to the advantage of empagliflozin compared to the control group. However, there is an effect modification for the NYHA class heart failure severity grade characteristic. For NYHA class II patients, there is a statistically significant difference in favour of empagliflozin. In contrast, there was no statistically significant difference between the treatment groups for patients of NYHA classes III/IV.

Discontinuation due to adverse events (AEs)

For the endpoint of discontinuation due to AEs, no statistically significant differences are found between the treatment groups.

Specific AEs

Urinary tract infection, reproductive system and breast disorders, *diabetic ketoacidosis*

In detail, there were no statistical differences between the treatment groups for the specific AE urinary tract infection (PT[9]) and reproductive system and breast disorders (SOC[10]). No data are available for the endpoint of diabetic ketoacidosis (PT, AE) because this event occurred in less than 1% of the study participants per treatment arm.

Renal and urinary disorders, hepatobiliary disorders

For the endpoints of renal and urinary disorders (SOC, SAE) and hepatobiliary disorders (SOC, SAE), there was a statistically significant difference between the treatment groups to the advantage of empagliflozin.

Atrial fibrillation

For the endpoint of atrial fibrillation (PT, SAE), there is a statistically significant difference between the treatment groups to the advantage of empagliflozin. However, an effect modification for the NYHA class heart failure severity grade characteristic is observed for this endpoint. For NYHA class II patients, there is a statistically significant advantage of empagliflozin over the comparator arm. In contrast, there was no statistically significant difference between the treatment arms for NYHA class III/IV patients.

Overall assessment / conclusion

The pharmaceutical company presents the placebo-controlled, double-blind, randomised EMPEROR-Reduced study for the early benefit assessment of empagliflozin for the new therapeutic indication for the treatment of adults with symptomatic, chronic heart failure with reduced ejection fraction. NYHA class II to IV patients with an LVEF[11] value ≤ 40% were studied, who also had to have increased NT-proBNP values (up to ≥ 2,500 pg/ml or ≥ 5,000 pg/ml for AF[12]).

The study medication empagliflozin, or placebo, was administered in addition to medicinal therapy for heart failure and other cardiovascular risk factors and comorbidities. This had to be done according to national and international recommendations. The therapy carried out in the study in the comparator arm largely corresponds to an optimised standard therapy for the treatment of heart failure and the underlying diseases, which was determined as the appropriate comparator therapy for the present therapeutic indication. The median treatment duration of the study was 1.2 years.

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

In the morbidity category, a statistically significant advantage of empagliflozin over the comparator arm is observed for the endpoint "total hospitalisation".

In terms of health status, as assessed by the EQ-5D VAS, there is a statistically significant advantage of ≥ 15 points improvement in week 52 for empagliflozin compared to the control arm, but this is no more than minor.

[9] PT: preferred term
[10] SOC: system organ class
[11] LEVF: left ventricular ejection fraction
[12] AF: atrial fibrillation or atrial flutter

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.

The combined endpoint "renal morbidity" cannot be assessed because the individual components are not comparable with each other in their severity grade, and an interpretation of the endpoint is therefore not possible. This endpoint is not used here.

In the category of health-related quality of life, data are available for the clinical sum score KCCQ-OSS in two operationalisations, which show different effects depending on the operationalisation. There are no statistically significant differences for the operationalisation as an improvement of ≥ 15%. For the improvement of ≥ 5 points, there is a statistically significant difference to the advantage of empagliflozin.

In the side effects category, there is a statistically significant difference for the overall rate of SAE, but this was only found to be a statistically significant advantage of empagliflozin over the comparator arm in NYHA class II patients due to effect modification by NYHA class. There were no statistically significant differences for NYHA class III/IV patients.
For the specific AEs, there was a statistically significant advantage of empagliflozin over the comparator arm for the endpoint "renal and urinary disorders, hepatobiliary disorders" for the total population. For the endpoint "atrial fibrillation", there was a statistically significant advantage of empagliflozin; due to an effect modification, there was only a statistically significant difference for empagliflozin compared to the control group in NYHA class II study participants. No statistically significant advantage was observed in NYHA class III/IV patients. There were no statistically significant differences in the other endpoints, including "discontinuation due to AEs".

In the overall assessment of the results based on the positive effects of empagliflozin in the avoidance of total hospitalisations, the improvement in quality of life as well as in the advantages in the category of side effects, in each case taking into account that the advantages in SAE and atrial fibrillation were only shown in NYHA class II patients, a minor additional benefit of empagliflozin compared with 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.

To be enrolled in the study, patients had to have increased NT-proBNP values. For example, in patients with an LVEF ≤ 36% to ≤ 40%, NT-proBNP had to be ≥ 2,500 pg/ml or ≥ 5,000 pg/ml for AF. This led to a restriction and selection of the study population, although the approved therapeutic indication does not provide for any limitations in this respect. For this reason, 36% of the screened study participants were excluded from enrolment in the study. Overall, it is therefore unclear to what extent the observed effects can be transferred without restriction to the total population in the therapeutic indication and thus, to the German health care context, including those patients in whom the NT-proBNP values required in the study are not achieved.

In addition, effect modification by the NYHA class characteristic was found for the positive effects of empagliflozin in the category of side effects in the overall rate of SAE and in the specific AE "atrial fibrillation". Consequently, a statically significant advantage is only shown for NYHA class II patients, but not those in NYHA classes III/IV. In this respect, the observed

effects in the category of side effects and the resulting effects for the total population in the therapeutic indication cannot be conclusively assessed.

In the implementation of the appropriate comparator therapy in the study, a sufficient approximation to the appropriate comparator therapy is assumed overall. However, there are some uncertainties about the extent to which all optimisation options were exhausted in the study, if a therapy adjustment was indicated.

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 empagliflozin: "for the treatment of adults with symptomatic, chronic heart failure with reduced ejection fraction".

For the patient population under consideration here: adults with symptomatic, chronic heart failure with reduced ejection fraction, 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 as well as the concomitant symptoms, was determined by the G-BA as an appropriate comparator therapy.

The double-blind, randomised EMPEROR-Reduced study was presented. This study investigated the administration of empagliflozin versus placebo, 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 (≥ 600 to ≥ 2,500 pg/ml or ≥ 1,200 to ≥ 5,000 pg/ml in AF).

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

Statically significant advantages for empagliflozin over the control arm were seen in the morbidity category for the endpoint "total hospitalisation". There were no statistically significant differences in the cardiovascular morbidity endpoints "myocardial infarction" and "stroke".

In the side effects category, there was an advantage of empagliflozin for the KCCQ-OSS clinical summary score, operationalised as an improvement of ≥ 5 points, which is assessed as minor. However, no statistically significant differences are found for the operationalisation as improvement by ≥ 15% of the KCCQ-OSS scale range.

In the side effects category, there was a statistically significant difference to the advantage of empagliflozin in the overall rate of SAE, with statistically significant results in favour of empagliflozin over the control arm only for NYHA class II study participants due to effect modification by NYHA class. The same applies to the events related to "atrial fibrillation"; an effect modification was also observed here and a statically significant advantage was only shown for NYHA class II patients for this endpoint. For "renal and urinary disorders, hepatobiliary disorders", there was an advantage of empagliflozin compared to the placebo arm for the total population.

Overall, the study has uncertainties especially regarding the restricted study population due to the required inclusion criteria with increased NT-proBNP values. In the overall assessment, a hint of minor additional benefit is determined.

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

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

For the determination of patient numbers, the G-BA takes into account the underlying data in the previous resolution in the therapeutic indication of chronic heart failure with reduced ejection fraction[13].

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 Jardiance (active ingredient: empagliflozin) at the following publicly accessible link (last access: 24 November 2021):

https://www.ema.europa.eu/en/documents/product-information/jardiance-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 December 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.

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 and the underlying diseases, such as hypertonia, cardiac arrhythmias, coronary 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.

[13] Resolution on dapagliflozin dated 20 May 2021 https://www.g-ba.de/beschluesse/4846/

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				
Empagliflozin	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	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Empagliflozin	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					
Empagliflozin 10 mg	100 FCT	€ 192.40	€ 1.77	€ 10.04	€ 180.59
+ Optimised standard therapy	different from patient to patient				
Appropriate comparator therapy					
Optimised standard therapy	different from patient to patient				
Abbreviations: 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.

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 7 June 2016, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 May 2020.

On 12 July 2021 the pharmaceutical company submitted a dossier for the benefit assessment of empagliflozin to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 13 July 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient empagliflozin.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 October 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 October 2021. The deadline for submitting written statements was 5 November 2021.

The oral hearing was held on 22 November 2021.

By letter dated 23 November 2021, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 10 December 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 was discussed at the session of the subcommittee on 21 December 2021, and the proposed resolution was approved.

At its session on 6 January 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	7 June 2016	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	26 May 2020	New implementation of the appropriate comparator therapy
Working group Section 35a	16 November 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	22 November 2021	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	30 November 2021 14 December 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	21 December 2021	Concluding discussion of the draft resolution
Plenum	6 January 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 January 2022

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

Prof. Hecken