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 with left ventricular ejection fraction LVEF > 40%)

of 15 September 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 in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

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

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

2. Key points of the resolution

The active ingredient 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 3 March 2022, 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 European 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 30 March 2022, i.e. no later than four weeks after the pharmaceutical company has been notified of the authorisation for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction

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

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 July 2022, 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.

Therapeutic indication of the resolution (resolution of 15.09.2022):

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for empagliflozin:

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

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

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

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

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

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

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

on 1. Currently, no medicinal products are specifically approved for the targeted treatment of heart failure with preserved ejection fraction (HFpEF) and mildly reduced ejection fraction (HFmrEF).

For the therapeutic indication "chronic heart failure", in particular for "chronic heart failure with reduced ejection fraction (HFrEF)", the following product classes or active ingredients are generally approved:

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

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

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

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

No resolutions are available for the therapeutic indication of chronic heart failure with preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF).

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

- Sacubitril/ valsartan (resolution of 16 June 2016)
- Dapagliflozin (resolution of 20 May 2021)
- Empagliflozin (resolution of 6 January 2022)
- Vericiguat (resolution of 3 March 2022)

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

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

While various active ingredients or product classes are approved for the treatment of heart failure with reduced ejection fraction (HFrEF) such as ACE inhibitors, ARBs, beta receptor blockers, mineralocorticoid receptor antagonists (MRA), etc., there are currently no medicinal products specifically approved for the treatment of heart failure with preserved reduction fraction (HFpEF) or with mildly reduced ejection fraction (HFmrEF).

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

In accordance with national and international guidelines, the G-BA considers patient-individual treatment to be appropriate, taking into account the type and severity of the comorbidities present. Accordingly, an optimised standard therapy for the treatment of symptomatic, chronic heart failure with preserved ejection fraction or mildly reducedejection fraction and the underlying diseases, such as hypertension, arrhythmias, coronary artery heart disease, diabetes mellitus, chronic kidney disease, dyslipoproteinaemia as well as the concomitant symptoms is determined as the appropriate comparator therapy.

In the pivotal study for the new therapeutic indication, empagliflozin was administered as an add-on to standard therapy. Therefore, it is anticipated that empagliflozin will be used in addition to standard therapy for the treatment of symptomatic chronic heart failure in HFpEF as well as HFmrEF. It is assumed that the patients in both study arms will be treated optimally: subject to a guideline-compliant patient-individual treatment of heart failure and underlying diseases or risk factors such as hypertension,

[2] Jardiance EPAR scientific conclusions and grounds for the variation to the terms of the marketing authorisation https://www.ema.europa.eu/en/documents/variation-report/jardiance-h-c-002677-ii-0060-epar-assessment-report-variation_en.pdf

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

[4] Resolution on the early benefit assessment of empagliflozin (chronic heart failure with preserved ejection fraction with LVEF ≤ 40%) of 06.01.2022 https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/716/#beschluesse

arrhythmias, kidney disease, dyslipoproteinaemia or diabetes mellitus as well as the concomitant symptoms, such as oedema. The adequate treatment of the underlying disease should be clearly documented in the dossier on the basis of the patient characteristics (e.g., HbA1c value, oedema, cardiac arrhythmias, etc.). The marketing authorisations and product information of the medicinal products are to be observed; deviations are to be justified separately.

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

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

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

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 preserved ejection fraction HFpEF (LVEF > 50%) and with mildly reduced ejection fraction HFmrEF (LVEF > 40 to 49%)

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-Preserved study, in which patients with chronic heart failure of NYHA classes II to IV with preserved ejection fraction, defined as LVEF > 40% were examined. For enrolment in the study, participants also had to have increased NT-proBNP[5] values, defined according to inclusion criteria as follows:

- NT-proBNP > 300 pg/ml, if neither atrial fibrillation nor atrial flutter was present
- NT-proBNP > 900 pg/ml in the presence of atrial fibrillation or atrial flutter.

In addition, patients had to either have structural cardiac disorder, such as enlargement of the left atrium and/or left ventricular hypertrophy, or have been hospitalised for heart failure within the 12 months prior to screening.

A total of 5,988 study participants were enrolled and randomised in a 1:1 ratio to the two study arms, empagliflozin versus placebo, and stratified according to the following criteria:

- Geographical region (North America, Latin America, Europe, Asia, Other)
- eGFR at the time of screening (<60 ml/ min/ 1.73 m², ≥ 60 ml/ min/ 1.73 m²)
- LVEF (< 50%; ≥ 50%).

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

One third of the adults in the study had an LVEF < 50%, two thirds had an LVEF ≥ 50%.

Half of the participants had type 2 diabetes mellitus or chronic kidney disease (CKD), defined as eGFR < 60 ml/ min/ 1.73 m² at the time of enrolment in the study. The extent to which these sub-populations overlap is unclear. About 13 % of the study population was diagnosed with type 2 diabetes mellitus only – without CKD.

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

The EMPEROR-Preserved study was event-controlled, with a median treatment duration of about 2 years. Patient-relevant results were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Uncertainty of the study population

Due to the above-mentioned inclusion criteria regarding increased NT-proBNP values, eligible patients with chronic heart failure and LVEF > 40%, who had already passed the screening phase, were additionally selected. This led to a limitation of the study population. Accordingly, 38% 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-Preserved study, patients with 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

Currently, there are no medicinal products for the targeted treatment of heart failure with preserved reduction fraction (HFpEF) and with mildly reducedejection fraction (HFmrEF). According to the guidelines, adequate treatment of relevant comorbidities - such as hypertension, arrhythmias, coronary artery heart disease, type 2 diabetes mellitus, chronic kidney disease and dyslipoproteinaemia – as well as concomitant symptoms should be ensured, especially in patients with HFpEF. In the presence of HFmrEF, the guidelines recommend treatment according to heart failure with reduced ejection fraction.

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

At the start of the study, the vast majority of patients were receiving anti-hypertensives. Thus, in about 80% of them, treatment with ACE inhibitors or ARBs was administered; in about 86%, beta receptor blockers or diuretics were used respectively. About 37% of patients received MRA therapy and about 2% of patients were treated with ARNI[6] both at the start of the study.

A query in the electronic case report form to the principal investigators also reported that almost all study participants received the best possible or best-tolerated treatment for heart

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

failure and concomitant treatment at the start of the study. Nevertheless, more than one third of the patients had inadequate blood pressure control (systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg) at the time of enrolment in the study.

In principle, adjustments to therapy were possible during the course of the study, but oral diuretics should be administered at a stable dose for at least one week before randomisation. Adjustments due to newly started or changed therapies during the study occurred in 3.8% in the intervention arm versus 4.3% in the comparator arm for ACE inhibitors or ARBs, and in 8.0% in the intervention arm versus 9.0% in the comparator arm for MRA. Adjustment of therapy with ARNI was experienced by 1.7% of participants in the intervention arm versus 2.6% in the comparator arm during the study.

With the exception of the study medication in the intervention arm, the use of SGLT-2 inhibitors was excluded from the study. Furthermore, there were no limitations regarding concomitant treatments.

With regard to the concomitant anti-diabetic treatment during the study, it is noted that almost 40% of the study participants were already receiving medicinal anti-diabetic therapy at the start of the study. The mean HbA1c value in the patients with diabetes at the start of the study was 7.2%. During the course of the study, 13.1% of subjects in the intervention arm and 15.8% in the comparator arm had their anti-diabetic therapy adjusted. However, there is no data available on the reasons why therapy was or was not adjusted or changed, and whether it was a new initiation, dose increase or dose reduction. Due to the exclusion of the use of SGLT-2 inhibitors in the comparator arm, these were not used in the control. The use of GLP-1 receptor agonists remained below 5% during the study.

Overall, the concomitant medicinal therapies administered in the study indicate that comorbidities were largely adequately treated in the subjects studied. Uncertainties remain, in particular, as to what extent an optimum blood pressure setting could be achieved in the course of the study, especially in the comparator arm, in more than one third of the study participants whose blood pressure was already inadequately adjusted at the start of the study.

Furthermore, any concomitant treatment at the doctor's discretion except for the use of SGLT-2 inhibitors could be performed in the comparator arm. The use of GLP-1 receptor agonists remained below 5% during the study.

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

Extent and probability of the additional benefit

Mortality

Overall mortality and cardiovascular death presented additionally

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

Morbidity

Hospitalisation due to heart failure

The endpoint "*hospitalisation due to heart failure*" was collected as time to first occurrence of adjudicated hospitalisation due to heart failure, occurrence of hospitalisation due to heart failure (first and repeat) and time to first occurrence of adjudicated hospitalisation due to heart failure with intensive care treatment. For the early benefit assessment, operationalisation over time to first event is leading.

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

For the endpoint *"hospitalisation due to heart failure"* for the time to first event, there is a statistically significant difference to the advantage of empagliflozin compared to the comparator arm. For the operationalisation "including repeat events", there was also a statistically significant difference to the advantage of empagliflozin compared to the comparator arm.

Total hospitalisation

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

For the endpoint "total hospitalisation" for the time to first event, the EMPEROR-Preserved study showed a statistically significant advantage for empagliflozin compared to the control arm. For the operationalisation "including repeat events", there was no statistically significant difference to the advantage of empagliflozin compared to the comparator arm.

Myocardial infarction and stroke

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

For the endpoint "myocardial infarction", there is an effect modification due to the gender characteristic. In women, there is a statistically significant difference to the disadvantage of empagliflozin. There were no statistically significant differences for men.

Renal morbidity

The endpoint "renal morbidity" was collected as part of a combined endpoint consisting of the following individual components:

- "Chronic dialysis",
- "Kidney transplant",

- "Sustained eGFR[7] < 15 ml/ min/ 1.73 m²" *(if eGFR ≥ 30 ml/ min/ 1.73 m² at the start of the study)* or "sustained eGFR < 10 ml/ min/ 1.73 m²" *(if eGFR < 30 ml/ min/ 1.73 m² at the start of the study),* or
- "Sustained reduction of eGFR by ≥ 40%".

The individual components "chronic dialysis", "kidney transplant", 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 half of the participants in the EMPEROR-Preserved study, the eGFR was ≥ 60 ml/ min/ 1.73 m². A relative "reduction of eGFR by ≥ 40%" with such high baseline values of eGFR is not comparable in terms of severity with the remaining individual components such as "chronic dialysis" or "kidney transplant". 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 and is only presented additionally.

There is no statistically significant difference between the treatment arms, neither for the combined renal endpoint nor for the respective individual components.

Acute kidney injury

In the EMPEROR-Preserved study, the time to first occurrence of acute kidney injury (collected as PT acute kidney injury according to the Medical Dictionary for Regulatory Activities[8]) was investigated as a secondary endpoint (efficacy). This endpoint is used for the early benefit assessment, but it only represents a partial aspect of the patient-relevant events of renal morbidity. No suitable data are available for a comprehensive mapping of renal morbidity (taking into account e.g., chronic kidney disease and dialysis).

For the endpoint of acute kidney injury (PT), there is a statistically significant difference between the treatment arms to the advantage of empagliflozin versus the comparator arm.

Health status

Health status was assessed in the study using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the improvement by ≥ 15 points at week 52, there is no statistically significant difference between the treatment arms.

Quality of life

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.

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

[7] eGFR: Estimated glomerular filtration rate
[8] MedDRA

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.

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 / hypertensive crisis / basal cell carcinoma

In detail, for the specific AE urinary tract infection (PT[9], AE), hypertensive crisis (PT, SAE) and basal cell carcinoma (PT, SAE), there was a statistically significant difference between the treatment groups to the advantage of empagliflozin compared to the control group.

Metabolism and nutrition disorders / musculoskeletal and connective tissue disorders / blood and lymphatic system disorders / respiratory, thoracic and mediastinal disorders

In detail, for the specific AEs of metabolism and nutrition disorders (SOC[10], SAE), musculoskeletal and connective tissue disorders (SOC; SAE), blood and lymphatic system disorders (SOC, SAE) and respiratory, thoracic and mediastinal disorders (SOC, SAE), there was a statistically significant difference between the treatment groups to the advantage of empagliflozin compared to the control group.

Reproductive system and breast disorders/ diabetic ketoacidosis

In detail, there was no statistically significant difference between the treatment groups for the specific AEs of reproductive system and breast disorders (SOC, AE) and diabetic ketoacidosis (PT, AE).

Overall assessment

The pharmaceutical company presents the placebo-controlled, double-blind, randomised EMPEROR-Preserved study for the early benefit assessment of empagliflozin for the new therapeutic indication for the treatment of adults with symptomatic, chronic heart failure with preserved ejection fraction (HFpEF) as well as mildly reduced ejection fraction (HFmrEF). NYHA class II to IV chronic heart failure patients with an LVEF[11] value ≥ 40% were studied, who also had to have increased NT-proBNP values (up to ≥ 300 pg/ ml or ≥ 900 pg/ ml for AF[12]). One third of the adults in the study had an LVEF < 50%, two thirds had an LVEF ≥ 50%. There was no statistically significant and relevant effect modification for the characteristic LVEF < 50% versus LVEF ≥ 50% at the start of the study.

[9] PT: preferred term
[10] SOC: System Organ Class
[11] LVEF: left ventricular ejection fraction
[12] AF: atrial fibrillation or atrial flutter

The study medication empagliflozin or placebo was administered in addition to medicinal background therapy for the treatment of heart failure and other underlying diseases, which according to the study protocol should be according to the best standard according to local guidelines.

The median treatment duration of the study was about 2 years.

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

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

In the morbidity category, a statistically significant advantage of empagliflozin over the comparator arm is observed for the endpoints "hospitalisation for heart failure", "total hospitalisation" and "acute kidney injury" (assessed as PT).

There are no statistically significant differences between the treatment arms for the other combined endpoints of the category 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, as well as for the "health status, collected using the EQ-5D VAS questionnaire".

In the category of health-related quality of life, data are available for the clinical sum score KCCQ-OSS. There are no statistically significant differences for the operationalisation as an improvement of ≥ 15%.

In the side effects category, there is a statistically significant difference for the overall rate of SAEs to the advantage of empagliflozin. For the endpoint of "discontinuation due to AEs", no statistically significant differences were found between the groups. Empagliflozin had positive effects in some specific AEs.

In the overall assessment of the results based on the positive effects of empagliflozin in the avoidance of hospitalisation due to heart failure, avoidance of total hospitalisations, in the endpoint of acute kidney injury as well as in the advantages in the category of side effects in SAEs, a minor additional benefit of empagliflozin compared to the appropriate comparator therapy is derived overall.

Reliability of data (probability of additional benefit)

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

There are uncertainties regarding the study population due to the inclusion criterion related to increased NT-proBNP levels as a condition for enrolment in the study. 38% of the screened study participants were excluded because of too low NT-proBNP values, although the approved therapeutic indication does not provide any limitations with regard to NT-proBNP values.

Furthermore, the study medication, empagliflozin versus placebo, should be administered in addition to medicinal background therapy for the treatment of heart failure as well as other

underlying diseases, which according to the study protocol should be administered according to the best standard according to guidelines.

In the present therapeutic indication, special importance is attached to the treatment of comorbidities. Already at the start of the study, more than one third of the patients had inadequately controlled blood pressure. It is unclear to what extent optimum blood pressure control could be achieved in these subjects during the course of the study, especially in the comparator arm.

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

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

2.1.4 Summary of the assessment

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

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

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

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

In the morbidity category for hospitalisation due to heart failure, total hospitalisation and acute kidney injury (assessed as PT), there was a statically significant advantage of empagliflozin over the control arm in each case. There were no statistically significant differences in the cardiovascular morbidity endpoints myocardial infarction and stroke.

In the health-related quality of life category, there are no statistically significant differences between the treatment arms.

In the side effects category, there was a statically significant difference to the advantage of empagliflozin in the overall rate of SAE. For the endpoint of discontinuation due to AEs, no statistically significant differences were found. Empagliflozin had positive effects in some specific AEs.

There is uncertainty in the selection of patients with increased NT-proBNP levels. Overall, the implementation of the appropriate comparator therapy is assumed to be sufficiently close to

the appropriate comparator therapy, although uncertainties remain in this regard as well. Therefore, the reliability of data is classified in the category "hint".

In the overall assessment of the results based on the positive effects of empagliflozin in the avoidance of hospitalisation due to heart failure, total hospitalisations, in the PT of acute kidney injury as well as in the advantages in the category of side effects, an overall hint for a minor additional benefit of empagliflozin is derived, taking into account the uncertainties mentioned.

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.

Overall, the information provided by the pharmaceutical company is subject to uncertainties, but is taken into account here despite the uncertainties.

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: 9 August 2022):

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: 15 August 2022).

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

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

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	Dose/ 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	€ 192.64	€ 1.77	€ 10.04	€ 180.83
+ optimised standard therapy	Different from patient to patient				
Appropriate comparator therapy					
Optimised standard therapy	Different from patient to patient				
Abbreviation: FCT = film-coated tablets					

LAUER-TAXE® last revised: 15 August 2022

Costs for additionally required SHI services:

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

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

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

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

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed on 15.02.2022.

On 30 March 2022, 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 1, sentence 2 VerfO.

By letter dated 31 March 2022 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 29 June 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2022. The deadline for submitting written statements was 22 July 2022.

The oral hearing was held on 8 August 2022.

By letter dated 9 August 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 26 August 2022.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 6 September 2022, and the proposed resolution was approved.

At its session on 15 September 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 June 2016	Determination of the appropriate comparator therapy
Working group Section 35a	15 February 2022	Review of the appropriate comparator therapy determined by the G-BA after issuing the positive opinion
Working group Section 35a	3 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2022	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents

Working group Section 35a	17 August 2022 31 August 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 September 2022	Concluding discussion of the draft resolution
Plenum	15 September 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 September 2022

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

Prof. Hecken