Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 6 January 2022, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as amended by the publication of the resolution of D. month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Empagliflozin in accordance with the resolution of 1 September 2016:

Empagliflozin

Resolution of: 6 January 2022
Entry into force on: 6 January 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 17 June 2021):

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

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Adults with symptomatic, chronic heart failure with reduced ejection fraction

Appropriate comparator therapy:

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

Extent and probability of the additional benefit of Empagliflozin over optimised standard therapy for symptomatic, chronic heart failure:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Adults with symptomatic, chronic heart failure with reduced ejection fraction

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	no statistically significant or relevant difference
Morbidity	↑	statistically significant advantage in total hospitalisation
Health-related quality of life	↑	improvement by ≥ 5 points in the KCCQ-OSS; no statistically significant difference for an improvement by ≥ 15 points (corresponds to 15%)
Side effects	↑	statistically significant advantage with SAE as well as in detail with specific AE

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

EMPEROR-Reduced study: Empagliflozin vs Placebo (each in addition to optimised standard therapy[2])

Mortality

Endpoint	Empagliflozin + optimised standard therapy		Placebo + optimised standard therapy		Intervention vs control
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI] p value[a] Absolute difference (AD)
Overall mortality	1863	n.d. 249 (13.4)	1867	n.d. 266 (14.2)	0.92 [0.77; 1.10]; 0.354
Cardiovascular death	1863	n.d. 187 (10.0)	1867	n.d. 202 (10.8)	0.92 [0.75; 1.12]; 0.413

[1] Data from the dossier assessment of the IQWiG (A21-93) and from the addendum (A21-93), unless otherwise indicated.
[2] In terms of patient-individual therapy of heart failure through the use of ACE inhibitors, angiotensin II receptor blockers (ARBs), sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonists (MRAs), diuretics, including the treatment of other cardiovascular risk factors and comorbidities

Morbidity

Endpoint	Empagliflozin + optimised standard therapy		Placebo + optimised standard therapy		Intervention vs control
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI] p value[a] *Absolute difference (AD)*
Total hospitalisation					
1. Event	1863	n.d. 688 (36.9)	1867	n.d. 796 (42.6)	0.82 [0.74; 0.90]; <0.001 *AD = 5.7%*
Presented additionally					
Including recurring events	*1863*	*Number of events 1364*	*1867*	*Number of events 1570*	*HR_{JFM}[b] [0.75; 1.12]; 0.413*
Myocardial infarction *(combined endpoint)*	1863	n.d. 19 (1.0)	1867	n.d. 18 (1.0)	1.04 [0.54; 1.98]; 0.917
Non-fatal	1863	n.d. 16 (0.9)	1867	n.d. 16 (0.9)	0.98 [0.49; 1.96]; 0.945
Lethal	1863	n.d. 3 (0.2)	1867	n.d. 2 (0.1)	1.51 [0.25; 9.10]; 0.650
Stroke *(combined endpoint)*	1863	n.d. 40 (2.1)	1867	n.d. 35 (1.9)	1.13 [0.72; 1.78]; 0.591
Non-fatal	1863	n.d. 34 (1.8)	1867	n.d. 24 (1.3)	1.40 [0.83; 2.37]; 0.206
Lethal	1863	n.d. 6 (0.3)	1867	n.d. 12 (0.6)	0.50 [0.19; 1.35]; 0.172
Presented additionally					
Renal morbidity (combined endpoint)[c]	*1863*	*n.d. 18 (1.0)*	*1867*	*n.d. 33 (1.8)*	*0.52 [0.29; 0.92]; <0.05 AD = 0.8%*
Sustained reduction of eGFR ≥ 50%	*1863*	*n.d. 18 (1.0)*	*1867*	*n.d. 22 (1.2)*	*n.d.*
ESRD	*1863*	*n.d. 4 (0.2)*	*1867*	*n.d. 9 (0.5)*	*n.d.*

Renal death	*1863*	*n.d.* *1 (0.1)*	*1867*	*n.d.* *2 (0.1)*	*n.d.*
Endpoint	**Empagliflozin + optimised standard therapy**		**Placebo + optimised standard therapy**		**Intervention vs control**
	N[d]	Patients with event n (%)	N[d]	Patients with event n (%)	RR [95% CI] p value[e] *Absolute difference (AD)*
Health status					
EQ-5D VAS improvement ≥ 15 points[f, g]	1733	495 (28.6)	1710	420 (24.6)	1.13 [1.02; 1.25]; 0.021 *AD = 4.0%*

Health-related quality of life

Endpoint	**Empagliflozin + optimised standard therapy**		**Placebo + optimised standard therapy**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[b] *Absolute difference (AD)*
KCCQ-OSS Improvement ≥ 15 points[f]	1740	445 (25.6)	1709	402 (23.5)	1.06 [0.95; 1.19]; 0.264
Domains (presented additionally)					
Physical limitations	*n.d.*	*n.d.*	*n.d.*	*n.d.*	*n.d.*
Symptoms (KCCQ-TSS)	*1740*	*466 (26.8)*	*1709*	*396 (23.2)*	*1.11 [0.99; 1.23]*
Social limitations	*n.d.*	*n.d.*	*n.d.*	*n.d.*	*n.d.*
Psychological limitations	*n.d.*	*n.d.*	*n.d.*	*n.d.*	*n.d.*
KCCQ-OSS Improvement ≥ 5 points[h]	1740	876 (50.3)	1709	800 (46.8)	1.07 [1.01; 1.14]; 0.035 *AD = 3.5%*
Domains (presented additionally)					
Physical limitations	*n.d.*	*n.d.*	*n.d.*	*n.d.*	*n.d.*
Symptoms (KCCQ-TSS)	*1740*	*812 (46.7)*	*1709*	*751 (43.9)*	*1.04 [0.98; 1.12]; 0.217*

Social limitations	*n.d.*	*n.d.*	*n.d.*	*n.d.*	*n.d.*
Psychological limitations	*n.d.*	*n.d.*	*n.d.*	*n.d.*	*n.d.*

Side effects

Endpoint	**Empagliflozin + optimised standard therapy**		**Placebo + optimised standard therapy**		**Intervention vs control**
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value[b] *Absolute difference (AD)*
Overall rates					
AE (presented additionally)[i]	*1863*	*1325 (71.1)*	*1863*	*1362 (73.1)*	–
SAE[i]	1863	540 (29.0)	1863	605 (32.5)	0.89 [0.81; 0.98]; 0.023 *AD = 3.5%*
NYHA II	1399	359 (25.7)	1399	432 (30.9)	0.83 [0.74; 0.94]; 0.002 *AD = 5.2%*
NYHA III/IV	464	181 (39.0)	464	173 (37.3)	1.05 [0.89; 1.23] 0.683
Total				Interaction:	0.038[k]
Discontinuation due to AEs	1863	322 (17.3)	1863	328 (17.6)	0.98 [0.85; 1.13]; 0.855
Specific adverse events					
Urinary tract infection (PT, AE)	1863	69 (3.7)	1863	72 (3.9)	0.96 [0.69; 1.32]; 0.866
Reproductive system and breast disorders (SOC, AE)	1863	57 (3.1)	1863	49 (2.6)	1.16 [0.80; 1.69]; 0.533
Diabetic ketoacidosis (PT, AE)[j]	n.d.	n.d.	n.d.	n.d.	n.d.

Endpoint	Empagliflozin + optimised standard therapy		Placebo + optimised standard therapy		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value[b] *Absolute difference (AD)*
Renal and urinary disorders (SOC, SAEs)	1863	71 (3.8)	1863	107 (5.7)	0.66 [0.49; 0.89]; 0.006 *AD = 1.9%*
Hepatobiliary disorders (SOC, SAEs)	1863	16 (0.9)	1863	30 (1.6)	0.53 [0.29; 0.98]; 0.040 *AD = 0.7%*
Atrial fibrillation (PT, SAEs)	1863	24 (1.3)	1863	44 (2.4)	0.55 [0.33; 0.89]; 0.015 *AD = 1.1%*
NYHA II	1399	16 (1.1)	1399	39 (2.8)	0.41 [0.23; 0.73]; 0.002 *AD = 1.7%*
NYHA III/IV	464	8 (1.7)	464	5 (1.1)	1,60 [0.53; 4.85]; 0.530
Total				Interaction:	0.026[k]

a. unless otherwise stated, HR, 95% CI and p value: Cox proportional hazards model; adjusted by region, sex, age, diabetes status, LVEF and eGFR value at start of study
b. HR_{JFM}, 95% CI and p value: Joint frailty model; adjusted by region, sex, age, diabetes status, LVEF and eGFR value at start of study; HR_{JFM} can be interpreted as treatment effect on the rate of (recurrent) hospitalisations
c. The combined endpoint includes sustained eGFR decrease of ≥ 50 %, ESRD and renal death. The single component ESRD includes chronic dialysis or renal transplantation or sustained eGFR < 15 ml/min/1.73 m².
d. Endpoints of the categories morbidity and health-related quality of life: missing values were replaced by means of LOCF (27% vs 26% in each case)
e. Endpoints of the categories morbidity and health-related quality of life: Log-link Poisson model with "robust variance estimators"; adjusted by region, sex, age, diabetes status, LVEF, eGFR value and baseline at start of study; endpoints of the category side effects: p value: IQWiG calculation, unconditional exact test (CSZ method according to Andrés et al, 1994).
f. Defined as an increase in score of ≥ 15 points compared to baseline at week 52 (scale range: 0-100 points)
g. The responder analyses submitted by the pharmaceutical company regarding the EQ-5D VAS with a response criterion of 10 or 7 points are presented additionally in the appendix of the benefit assessment by IQWiG.
h. Defined as an increase in score of ≥ 5 points compared to baseline at week 52 (scale range: 0-100 points)
i. Without consideration of the following (disease-related) events: Death from any cause, hospitalisation for heart failure, myocardial infarction, stroke, non-fatal transient ischaemic attack, atrial fibrillation

Endpoint	Empagliflozin + optimised standard therapy		Placebo + optimised standard therapy		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value[b] *Absolute difference (AD)*
(severe), acute kidney failure (severe), unstable angina pectoris j. In module 4 A, no data are available for this endpoint as the event occurred in less than 1% of patients per treatment arm k. Breslow-Day test for homogeneity of odds ratios AD: absolute difference; eGFR: estimated glomerular filtration rate; EQ-5D: European Quality of Life Questionnaire - 5 Dimensions; ESRD: end-stage kidney disease; HR: hazard ratio; JFM: joint frailty Model; n.d.: no data available; KCCQ: Kansas City Cardiomyopathy Questionnaire; CI: confidence interval; LOCF: last observation carried forward; LVEF: left ventricular ejection fraction; n: number of patients with (at least 1) event; N: number of patients evaluated; OSS: overall summary score; RCT: randomised controlled trial; RR: relative risk; TSS: total symptom score; VAS: visual analogue scale					

2. Number of patients or demarcation of patient groups eligible for treatment

Adults with symptomatic, chronic heart failure with reduced ejection fraction

approx. 2,061,700 to 2,273,000 patients

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

4. Treatment costs

Adults with symptomatic, chronic heart failure with reduced ejection fraction

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Empagliflozin	€ 659.15
+ Optimised standard therapy	different from patient to patient
Appropriate comparator therapy:	
Optimised standard therapy	different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 December 2021)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 6 January 2022.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 6 January 2022

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

Prof. Hecken