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 with left ventricular ejection fraction LVEF > 40%)

of 15 September 2022

At its session on 15 September 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 last 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 6 January 2022:**

Empagliflozin

Resolution of: 15 September 2022
Entry into force on: 15 September 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 3 March 2022):

Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure.

Therapeutic indication of the resolution (resolution of 15 September 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%)

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

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

Extent and probability of the additional benefit of empagliflozin compared with optimised standard therapy for symptomatic chronic heart failure with preserved ejection fraction or mildly reduced ejection fraction and underlying conditions:

Hint for a minor additional benefit

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.

[1] Data from the dossier assessment of the IQWiG (A22-39) and from the addendum (A22-86), unless otherwise indicated.

Morbidity	↑	Benefit in hospitalisation for heart failure, total hospitalisation and acute kidney injury, respectively.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↑	Advantage in SAE. In detail, advantages in specific AEs.

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

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

EMPEROR-Preserved 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	2997	n.d. 422 (14.1)	2991	n.d. 427 (14.3)	1.00 [0.87; 1.15]; 0.989
Cardiovascular death *(presented additionally)*	2997	n.d. 219 (7.3)	2991	n.d. 244 (8.2)	0.91 [0.76; 1.09]; 0.295

[2] In the sense of patient-individual treatment of the underlying diseases as well as the concomitant symptoms according to the therapy standard in accordance with local guidelines and recommendations for heart failure and, if applicable, diabetes mellitus through the use of anti-hypertensives, antithrombotics, anti-diabetics and lipid-lowering agents.

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)*
Hospitalisation due to heart failure 1st event	2997	n.d. 259 (8.6)	2991	n.d. 352 (11.8)	0.71 [0.60; 0.83]; < 0.001 *AD = 3.2 %*
including recurring events (presented additionally)	*2997*	*Number of events 407*	*2991*	*Number of events 541*	*HR_{JFM}[b] 0.73 [0.61; 0.88]; 0.001*
Total hospitalisation 1st event	2997	n.d. 1271 (42.4)	2991	n.d. 1340 (44.8)	0.92 [0.85; 0.99]; 0.032 *AD = 2.4 %*
including recurring events (presented additionally)	*2997*	*Number of events 2566*	*2991*	*Number of events 2769*	*HR_{JFM}[b] 0.93 [0.85; 1.01]; 0.101*
Myocardial infarction *(composite endpoint)*	2997	n.d. 49 (1.6)	2991	n.d. 40 (1.3)	1.23 [0.81; 1.86]; 0.338
non-lethal	2997	n.d. 42 (1.4)	2991	n.d. 36 (1.2)	1.17 [0.75; 1.83]; 0.487
lethal	2997	n.d. 5 (0.2)	2991	n.d. 3 (0.1)	1.71 [0.41; 7.16]; 0.463
Stroke *(composite endpoint)*	2997	n.d. 92 (3.1)	2991	n.d. 84 (2.8)	1.10 [0.82; 1.47]; 0.539
non-lethal	2997	n.d. 78 (2.6)	2991	n.d. 69 (2.3)	1.13 [0.82; 1.56]; 0.463
lethal	2997	n.d. 16 (0.6)	2991	n.d. 17 (0.6)	0.95 [0.48; 1.89]; 0.893
Renal morbidity (composite endpoint)	*2997*	*n.d. 108 (3.6)*	*2991*	*n.d. 112 (3.7)*	*0.95 [0.73; 1.24]; 0.724*

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)*
(presented additionally)					
Chronic dialysis	*2997*	*n.d.* *11 (0.4)*	*2991*	*n.d.* *11 (0.4)*	*0.92* *[0.40; 2.13];* *0.849*
Kidney transplant	*2997*	*n.d.* *0 (0)*	*2991*	*n.d.* *0 (0)*	*1.00* *[n.c.; n.c.];* *n.c.*
Sustained eGFR[c] < 15 / < 10 ml/min/ 1.73m²	*2997*	*n.d.* *10 (0.3)*	*2991*	*n.d.* *8 (0.3)*	*1.01* *[0.39; 2.61];* *0.990*
Sustained reduction of eGFR ≥ 40%	*2997*	*n.d.* *99 (3.3)*	*2991*	*n.d.* *107 (3.6)*	*0.92* *[0.70; 1.21];* *0.547*
Acute kidney injury PT (secondary endpoint)[i]	2997	n.d. 97 (3.2)	2991	n.d. 131 (4.4)	0.73 [0.56; 0.95]; 0.019[j] *AD = 1.2 %*
PT, AE (presented additionally)[k]	*2996*	*n.d.* *81 (2.7)*	*2989*	*n.d.* *107 (3.6)*	*RR: 0.76* *[0.57; 1.00][l];* *0.053[m]*
PT, SAE (presented additionally)[k]	*2996*	*n.d.* *81 (2.7)*	*2989*	*n.d.* *107 (3.6)*	*RR: 0.76* *[0.57; 1.00][l];* *0.053[m]*
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]
Health status					
EQ-5D VAS improvement ≥ 15 points[f]	2886	668 (23.1)	2868	604 (21.1)	1.05 [0.96; 1.15]; 0.270

Health-related quality of life

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)*
KCCQ-OSS Improvement ≥ 15 points[f]	2884	642 (22.3)	2867	576 (20.1)	1.05 [0.96; 1.15]; 0.296
Domains (presented additionally)					
Physical limitations	*2829*	*669 (23.6)*	*2823*	*652 (23.1)*	*1.01 [0.92; 1.10]; 0.840*
Psychological quality of life	*2884*	*964 (33.4)*	*2867*	*896 (31.3)*	*1.03 [0.96; 1.11]; 0.360*
Social limitations	*2686*	*765 (28.5)*	*2700*	*726 (26.9)*	*1.02 [0.94; 1.11]; 0.584*
Symptoms (KCCQ-TSS)[f]	*2884*	*754 (26.1)*	*2867*	*648 (22.6)*	*1.08 [0.99; 1.18] 0.066*

Side effects

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)*
Overall rates					
AE (presented additionally)[g]	*2996*	*2512 (83.8)*	*2989*	*2507 (83.9)*	–
SAE[g]	2996	1157 (38.6)	2989	1243 (41.6)	0.93 [0.87; 0.99]; 0.019[h] *AD = 3.0 %*
Discontinuation due to AEs	2996	571 (19.1)	2989	551 (18.4)	1.03 [0.93; 1.15]; 0.536[h]
Specific adverse events					
Urinary tract	2996	236 (7.9)	2989	181 (6.1)	1.30

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)*
infection (PT, AE)					[1.08; 1.57]; 0.006[h] *AD = 1.8 %*
Reproductive system and breast disorders (SOC, AE)	2996	116 (3.9)	2989	117 (3.9)	0.99 [0.77; 1.27]; 0.932[h]
Diabetic ketoacidosis (PT, AE)	2996	3 (0.1)	2989	2 (0.1)	1.50 [0.25; 8.95]; 0.753
Metabolism and nutrition disorders (SOC, SAE)	2996	84 (2.8)	2989	114 (3.8)	0.74 [0.56; 0.97]; 0.029 *AD = 1.0 %*
Musculoskeletal and connective tissue disorders (SOC, SAE)	2996	53 (1.8)	2989	76 (2.5)	0.70 [0.49; 0.98]; 0.040 *AD = 0.7 %*
Blood and lymphatic system disorders (SOC, SAE)	2996	33 (1.1)	2989	60 (2.0)	0.55 [0.36; 0.84]; 0.005 *AD = 0.9 %*
Respiratory, thoracic and mediastinal disorders (SOC, SAE)	2996	113 (3.8)	2989	151 (5.1)	0.75 [0.59; 0.95]; 0.016 *AD = 1.3 %*
Hypertensive crisis (PT, SAE)	2996	13 (0.4)	2989	32 (1.1)	0.41 [0.21; 0.77]; 0.004 *AD = 0.7 %*
Basal cell carcinoma (PT, SAE)	2996	17 (0.6)	2989	32 (1.1)	0.53 [0.29; 0.95]; 0.031 *AD = 0.5 %*

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. sustained eGFR < 15 ml/min/1.73 m² in patients with an eGFR ≥ 30 ml/min/1.73 m² at the start of the study or sustained eGFR < 10 ml/min/1.73 m² in patients with an eGFR < 30 ml/min/1.73 m² at the start of the study

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)*

d. Endpoints of the categories morbidity and health-related quality of life: missing values were replaced by means of LOCF (KCCQ-OSS: 14.3%; EQ-5D VAS: 13.9% vs 13.7%)
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 the respective baseline at the start of the study; endpoints of the category side effects: RR, 95% CI (asymptotic) and p value (unconditional exact test [CSZ method according to Andrés et al.,1994), each calculated by IQWiG.
f. Defined as an increase in score of ≥ 15 points compared to baseline at week 52 (scale range: 0-100 points). Higher (increasing) values mean an improvement in health status / symptomatology / health-related quality of life
g. Without consideration of the following (disease-related) events: Death from any cause, hospitalisation for heart failure, myocardial infarction, stroke, transient ischaemic attack, atrial fibrillation (severe), acute kidney failure (severe), unstable angina pectoris
h. Chi-square test
i. collected as secondary endpoint via the PT acute kidney injury according to MedDRA; a follow-up of 30 days is assumed
j. Result of the IQWiG calculation of RR, 95% CI (asymptotic) and p value (unconditional exact test, CSZ method according to Andrés). 0.74 [0.57; 0.96]; 0.021
k. recorded as AE or SAE via the PT acute kidney injury according to MedDRA; follow-up 7 days
l. Cochran-Mantel-Haenszel method
m. IQWiG calculation: unconditional exact test (CSZ method according to Andrés)

Abbreviations:

AD: absolute difference; eGFR: estimated glomerular filtration rate; EQ-5D: European Quality of Life Questionnaire - 5 Dimensions; 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; n.c.: not calculable; 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 preserved ejection fraction HFpEF (LVEF > 50%) and with mildly reduced ejection fraction HFmrEF (LVEF > 40 to 49%)

approx. 1,270,000 to 1,400,000 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: 9 August 2022):

https://www.ema.europa.eu/en/documents/product-information/jardiance-epar-product-information_en.pdf

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Empagliflozin	€ 660.03
+ 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: 15 August 2022)

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 15 September 2022.

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

Berlin, 15 September 2022

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

Prof. Hecken