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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Dapagliflozin (new therapeutic indication: chronic heart failure with left ventricular ejection fraction LVEF > 40%)

of 17 August 2023

At its session on 17 August 2023, 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 Dapagliflozin in accordance with the resolution of 16 June 2022:

Dapagliflozin

Resolution of: 17 August 2023
Entry into force on: 17 August 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 3 February 2023):

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

Therapeutic indication of the resolution (resolution of 17 August 2023):

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 dapagliflozin:

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 dapagliflozin 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.
Morbidity	↑	Advantage in hospitalisation due to heart failure
Health-related quality of life	↑	Advantage in health-related quality of life (KCCQ-OSS)
Side effects	↔	No relevant difference for the benefit assessment.
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 ∅: No data available. n.a.: not assessable		

DELIVER study: Dapagliflozin vs placebo (each in addition to optimised standard therapy[2])

Mortality

Endpoint	Dapagliflozin + 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	3,131	n.d. 497 (15.9)	3,132	n.d. 526 (16.8)	0.94 [0.83; 1.07]; 0.343
Cardiovascular death (presented additionally)	*3,131*	*n.d.* *231 (7.4)*	*3,132*	*n.d.* *261 (8.3)*	*0.88 [0.74; 1.05]; 0.168*

[1] Data from the dossier assessment of the IQWiG (A23-11) and from the addendum (A23-71), unless otherwise indicated.

[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 the respective comorbidities through the use of anti-hypertensive drugs, antithrombotics, anti-diabetics and lipid-lowering agents.

Morbidity[b]

Endpoint	Dapagliflozin + 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	3,131	n.d. 329 (10.5)	3,132	n.d. 418 (13.3)	0.77 [0.67; 0.89]; < 0.001 *AD = 2.8%*
including recurring events (presented additionally)	*3,131*	*Number of events 508*	*3,132*	*Number of events 707*	*Rate ratio [95% CI]; p value[c] 0.72 [0.60; 0.85]; < 0.001*
Total hospitalisation 1st event	3,131	n.d. 1210 (38.6)	3,132	n.d. 1251 (39.9)	0.94 [0.86; 1.01]; 0.101
including recurring events (presented additionally)		*Number of events 2,224*		*Number of events 2,479*	*Rate ratio [95% CI]; p value[c] 0.90 [0.82; 0.98]; 0.015*
Myocardial infarction *(composite endpoint)*	3,131	n.d. 83 (2.7)	3,132	n.d. 81 (2.6)	1.02 [0.75; 1.39]; 0.890
non-fatal	3,131	n.d.	3,132	n.d.	n.d.
fatal[d]	3,131	n.d. 12 (0.4)	3,132	n.d. 15 (0.5)	0.80 [0.37; 1.70]; 0.560
Stroke *(composite endpoint)*	3,131	n.d. 115 (3.7)	3,132	n.d. 109 (3.5)	1.05 [0.81; 1.37]; 0.706
non-fatal	3,131	n.d.	3,132	n.d.	n.d.
fatal[d]	3,131	n.d. 28 (0.9)	3,132	n.d. 25 (0.8)	1.12 [0.65; 1.92]; 0.682

Renal morbidity (presented additionally)					
Sustained reduction of eGFR ≥ 50%	3,131	n.d. 44 (1.4)	3,132	n.d. 46 (1.5)	0.96 [0.63; 1.45] 0.830
Doubling of serum creatinine level accompanied by eGFR ≤ 45 ml/min/ 1.73 m²	3,131	n.d. 35 (1.1)	3,132	n.d. 36 (1.1)	0.98 [0.62; 1.56] 0.932

Endpoint	**Dapagliflozin + optimised standard therapy**		**Placebo + optimised standard therapy**		**Intervention vs control**
	N[e]	Median time to event in months [95% CI] Patients with event n (%)	N[e]	Median time to event in months [95% CI] Patients with event n (%)	RR [95% CI] p value[f] *Absolute difference (AD)*
Health status					
EQ-5D VAS[g]	2,498	682 (27.3)	2,536	633 (25.0)	1.09 [1.00; 1.20]; 0.059[i]
PGIS[h]	2,842	2,154 (75.8)	2,841	2,088 (73.5)	1.03 [1.00; 1.06]; 0.047[i] *AD = 2.3%*

Health-related quality of life[b]

Endpoint	Dapagliflozin + optimised standard therapy		Placebo + optimised standard therapy		Intervention vs control
	N[e]	Median time to event in months [95% CI] Patients with event n (%)	N[e]	Median time to event in months [95% CI] Patients with event n (%)	RR [95% CI] p value[f] *Absolute difference (AD)*
KCCQ-OSS[g]	2,842	855 (30.1)	2,837	769 (27.1)	1.11 [1.02; 1.21]; 0.013[i] *AD = 3.0%*
Domains (presented additionally)					
Physical limitations	2,792	843 (30.2)	2,792	747 (26.8)	1.13 [1.04; 1.23]
Psychological quality of life	2,842	1,147 (40.4)	2,837	1053 (37.1)	1.02 [0.99; 1.04]
Social limitations	2,669	884 (33.1)	2,664	845 (31.7)	1.03 [0.98; 1.09]
Symptoms (KCCQ-TSS)	2,842	920 (32.4)	2,837	857 (30.2)	1.07 [0.99; 1.16]

Side effects[b]

Endpoint	Dapagliflozin + optimised standard therapy		Placebo + optimised standard therapy		Intervention vs control
	N[e]	Median time to event in months [95% CI] Patients with event n (%)	N[e]	Median time to event in months [95% CI] Patients with event n (%)	RR [95% CI] p value[f] *Absolute difference (AD)*
Overall rates					
AE (presented additionally)	Endpoint not assessed[j]				
SAE[k]	3,126	947 (30.3)	3,127	975 (31.2)	0.97 [0.90; 1.05]; 0.443
Discontinuation due to AEs[l]	3,126	183 (5.9)	3,127	181 (5.8)	1.01 [0.83; 1.24]; 0.907
Specific adverse events					
Urinary tract	No suitable data[j]				

infection (PT, AE)					
Genital infection (PT, AE)	No suitable data[j]				
Diabetic ketoacidosis[m] (AE)	3,126	2 (< 0.1)	3,127	0	5.00 [0.24; 104.1]; 0.172[n]
Gastrointestinal disorders (SOC, SAE)	3,126	86 (2.8)	3,127	147 (4.7)	0.59 [0.45; 0.76]; < 0.001[n] *AD = 1.9%*
COVID-19 (PT, SAE)	3,126	183 (5.9)	3,127	144 (4.6)	1.27 [1.03; 1.57]; 0.027[n] *AD = 1.3%*

a. Effect, CI and p value: Cox proportional hazards model stratified by type 2 diabetes mellitus status at randomisation.
b. Includes all events from the first dose of the study medication, regardless of whether the patient was on treatment with the study medication or not when the event occurred.
c. Effect, CI and p value: Proportional rates model according to Lin-Wei-Yang-Ying, stratified by type 2 diabetes mellitus status at randomisation.
d. Adjudicated by an endpoint committee.
e. Endpoints of the categories morbidity and health-related quality of life: Number of patients for whom the value at the start of the study and at least one value after the start of the study were available. Missing values for the end-of-study visit were replaced using LOCF.
f. Effect, CI and p value: logistic regression model with log link, adjusted for type 2 diabetes mellitus status at the start of the study.
g. Improvement at the end-of-study visit; percentage of patients with an increase in score of ≥ 15 points compared to the start of the study at the end-of-study visit within 6 weeks of reaching the planned number of events of the primary endpoint; scale range from 0 to 100, higher (increasing) values mean an improvement in health status/ health-related quality of life.
h. Stability (no deterioration at the end-of-study visit); percentage of patients without an increase in score of ≥ 1 point on a 6-point scale (from 1 "no symptoms" to 6 "very severe symptoms") compared to the start of the study at the end-of-study visit
i. Unadjusted model due to convergence problems
j. Only non-serious AEs that led to a dose reduction/ discontinuation/ interruption of the study medication, were potentially also recorded as efficacy endpoints or belonged to a selection of AEs predefined by the pharmaceutical company were recorded.
k. Without taking into account the following events, which were defined as secondary complications by the pharmaceutical company in Module 4 A: Death from any cause, hospitalisation for heart failure, myocardial infarction, stroke, transient ischaemic attack, atrial fibrillation, acute kidney failure and unstable angina pectoris.
l. Including events that the pharmaceutical company defined as secondary complications
m. Probable and definite diabetic ketoacidosis adjudicated by an endpoint committee were analysed.
n. IQWiG calculation, 95% CI asymptotic, unconditional exact test (CSZ method according to Andrés)

COVID-19: coronavirus disease 2019; HR: hazard ratio; n. d.: no data available; KCCQ: Kansas City Cardiomyopathy Questionnaire; CI: confidence interval; LOCF: last observation carried forward; n: number of patients with (at least 1) event; N: number of patients evaluated; OSS: Overall Summary Score; PGIS: Patient Global Impression of Severity; PT: preferred term; PC: pharmaceutical company; RR: relative risk; SOC: system organ class; SAE: serious adverse event; TSS: Total Symptom Score; AE: adverse event; 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 Forxiga (active ingredient: dapagliflozin) at the following publicly accessible link (last access: 12 July 2023):

https://www.ema.europa.eu/en/documents/product-information/forxiga-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:	
Dapagliflozin	€ 883.67
+ 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 August 2023)

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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 following medicinal products with new active ingredients that can be used in a combination therapy with dapagliflozin in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

– Empagliflozin (Jardiance).

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. In Annex XIIa of the Pharmaceuticals Directive, the following information shall be added in alphabetical order:

"Active ingredient of the assessed medicinal product

Dapagliflozin

Resolution according to Section 35a paragraph 3 SGB V from

17 August 2023

Therapeutic indication of the resolution

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

Patient group

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

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names)

– Empagliflozin (Jardiance).

Period of validity of the designation (since... or from... to)

Since 17 August 2023"

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 17 August 2023.

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

Berlin, 17 August 2023

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

Prof. Hecken