Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Dapagliflozin (new therapeutic indication: chronic heart failure)

of 20 May 2021

At its session on 20 May 2021, 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 on DD 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 19 December 2019:

Dapagliflozin

Resolution of: 20 May 2021
Entry into force on: 20 May 2021
BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 3 December 2020):

"In heart failure, Forxiga is used in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction."

Therapeutic indication of the resolution (resolution from the 20 May 2021):

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 of care for the treatment of symptomatic chronic heart failure and underlying conditions such as hypertonia, arrhythmias, coronary artery disease, diabetes mellitus, hypercholesterolaemia and associated symptoms

Magnitude and likelihood of additional benefit of dapagliflozin over optimised standard therapy for symptomatic chronic heart failure:

Hint of a considerable 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	↑	Advantage in all-cause mortality as well as in cardiovascular mortality (presented additionally). For both endpoints, there is an effect modification with respect to the severity of heart failure according to NYHA class: for patients with NYHA class II, there is a benefit in

[1] Data from the dossier evaluation of the IQWiG (A20-113) and from the addendum (A21-44), unless otherwise indicated.

		all-cause mortality and cardiovascular mortality, while for patients with NYHA class III/IV, there is no benefit.
Morbidity	↑	Benefits for total hospitalisation.
Health-related quality of life	↑	Advantage in health-related quality of life (KCCQ-OSS).
Side effects	↑	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 is no usable data for the benefit assessment.
n.a.: not assessable

DAPA-HF 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	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI] p value[a] Absolute difference (AD)[i]
All-cause mortality	2373	276 (11.6)	2371	329 (13.9)	0.83 [0.71; 0.97]; 0.022 AD ≤ 2.3%
NYHA II	1606	125 (7.8)	1597	192 (12.0)	0.64 [0.51; 0.80]; < 0.001
NYHA III/IV	767	151 (19.7)	774	137 (17.7)	1.12 [0.89; 1.42] 0.326

[2] patient-specific optimised standard therapy of heart failure according to locally accepted guidelines (ACE inhibitors, angiotensin II receptor blockers (ARB), sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonists (MRA), diuretics).

Total				*Interaction:*	*p < 0.001*
Cardiovascular Mortality[v] *(shown additionally)*	2373	227 (9.6)	2371	273 (11.5)	0.82 [0.69; 0.98]; 0.029[b] AD ≤ 2.9%

Morbidity

Endpoint	**Dapagliflozin + optimised standard therapy**		**Placebo + optimised standard therapy**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI] p value[a] Absolute difference (AD)[i]
Total hospitalisation	2373	785 (33.1)	2371	886 (37.4)	0,88 [0.82; 0.95]; 0.002[h] AD = 4.3 %
Myocardial Infarction[f]	2373	46 (1.9)	2371	41 (1.7)	1.11 [0.73; 1.69]; 0.625
non-fatal	2373	38 (1.6)	2371	33 (1.4)	1.14 [0.71; 1.82]; 0.583
fatal	2373	8 (0.3)	2371	8 (0.3)	0.99 [0.37; 2.63]; 0.982
Strokes[g]	2373	42 (1.8)	2371	46 (1.9)	0.90 [0.59; 1.37]; 0.629
non-fatal	2373	36 (1.5)	2371	37 (1.6)	0.96 [0.61; 1.52]; 0.865
fatal	2373	8 (0.3)	2371	9 (0.4)	0.88 [0.34; 2.28]; 0.791
renal morbidity[c]	2373	28 (1.2)	2371	39 (1.6)	0.71 [0.44; 1.16]; 0.168[d]
sustained eGFR decrease of 50%	2373	14 (0.6)	2371	23 (1.0)	0.60 [0.31; 1.16]; 0.126[d]
ESRD	2373	16 (0.7)	2371	16 (0.7)	1.00 [0.50; 1.99];

Endpoint	Dapagliflozin + optimised standard therapy			Placebo + optimised standard therapy			Intervention vs control
	N	Patients with event n (%)		N	Patients with event n (%)		HR [95% CI] p value[a] Absolute difference (AD)[i]
							0.995[d]
renal death	2372	0 (0)		2371	1 (0)		–[e]
health status							
PGIC							
no deterioration in PGIC[n]	2165	2024 (93.5)		2141	1990 (92.9)		1.01 [0.99; 1.02]; 0.506[o]
PGIS							
no deterioration in PGIS[n]	2237	1745 (78.0)		2211	1655 (74.9)		1.04 [1.01; 1.08]; 0.013[p] AD = 3.1 %
	N[q]	Values at start of study MV (SD)	Change at end of study MW[r] (SE)	N[q]	Values at start of study MV (SD)	Change at end of study MW[r] (SE)	MD [95 %-CI]; p-value[r]
EQ-5D VAS[s]							
	2069	67.93 (17.53)	1.98 (0.27)	2064	68.20 (17.18)	1.15 (0.27)	0.83 [0.08; 1.58]; 0.029 Hedges' g: 0.07 [0.01; 0.13]

Health-related quality of life

Endpoint	Dapagliflozin + optimised standard therapy		Placebo + optimised standard therapy		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI] p value[a]
KCCQ-OSS					

Improvement of 15 points (corresponds to 15% of the scale range)					
KCCQ-OSS	2234	958 (42.9)	2209	863 (39.1)	1,10 [1.03; 1.18]; 0.006[t] AD = 3.8 %
Domains (presented additionally)					
Physical limitations	no data				
Symptomatology[u]	2234	1192 (53.4)	2209	1070 (48.4)	1,11 [1.05; 1.18]
social limitations	no data				
psychological quality of life	no data				
Improvement by 5 points					
KCCQ-OSS	2234	1129 (50.5)	2209	1010 (45.7)	1.08 [1.02; 1.14]; 0.009[t] AD = 4.8 %
Domains (presented additionally)					
Physical limitations	no data				
Symptomatology[u]	2234	1245 (55.7)	2209	1119 (50.7)	1.08 [1.03; 1.14]
social limitations	no data				
psychological quality of life	no data				

Side effects

Endpoint	**Dapagliflozin + optimised standard therapy**		**Placebo + optimised standard therapy**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value[j] Absolute difference (AD)[i]
Total adverse events (presented additionally)					
Endpoint not surveyed[k]					
Serious adverse events (SAE[l])					

	2368	659 (27.8)	2368	728 (30.7)	0.90 [0.83; 0.99]; 0.025 AD = 2.9 %
Therapy discontinuation because of adverse events					
	2368	111 (4.7)	2368	116 (4.9)	0.96 [0.74; 1.23]; 0.733
Specific adverse events					
Urinary tract infection (PT, AEs)	2368	44 (1.9)	2368	47 (2.0)	0.94 [0.62; 1.41]; 0.750
Genital and mammary gland diseases (SOC, AEs)	2368	33 (1.4)	2368	33 (1.4)	1.00 [0.62; 1.62]; 0.999
Diabetic ketoacidosis (PT, AEs)	2368	3 (0.1)	2368	0 (0)	7.00 [0.36; 135.44]; 0.097[m]
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	2368	57 (2.4)	2368	88 (3.7)	0.65 [0.47; 0.90]; 0.010 AD = 1.3 %

a. Unless otherwise stated: Cox-Proportional-Hazards-Model (score test) stratified by diabetes mellitus type 2 status at randomisation
b. Cox-Proportional-Hazards-Model (score test) stratified by diabetes mellitus type 2 status at randomisation, adjusted for previous hospitalisation for heart failure
c. The combined endpoint includes sustained eGFR decrease of ≥ 50%, ESRD and renal death.
d. Cox-Proportional-Hazards-Model (score test) stratified by diabetes mellitus type 2 status at randomisation, adjusted for eGFR at time of enrolment
e. Because no deaths occurred in one study arm, HR cannot be meaningfully estimated.
f. The combined endpoint includes nonfatal and fatal myocardial infarctions.
g. The combined endpoint includes nonfatal and fatal strokes.
h. Logistic regression with log link and treatment arm and diabetes mellitus type 2 status at baseline as covariates
i. An Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
j. Logistic regression with log-link, adjusted for diabetes mellitus type 2 status at time of enrolment
k. Only non-serious AEs that led to treatment discontinuation or dose adjustment or belonged to a selection of AEs predefined by the company were recorded.
l. without events adjudicated to the primary cardiovascular endpoint, myocardial infarction, stroke, or secondary and exploratory renal endpoints
m. IQWiG calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test, CSZ method according to Andrés et al., 1994).
n. no worsening on a 7-point (PGIC; “much better” to “much worse”) or 6-point scale (PGIS; “no symptoms” to “very severe symptoms”)
o. Logistic regression with log link and treatment arm and diabetes mellitus type 2 status at baseline as covariates
p. Quadratic calculation
q. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at baseline (possibly at other times) can be based on other patient numbers.
r. MMRM adjusted for treatment arm, value at baseline, visit, and interaction between treatment arm and visit
s. Higher (increasing) values mean better well-being/health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention.
t. Logistic regression with log link and treatment arm, KCCQ score at baseline, and diabetes mellitus type 2 status at baseline as covariates
u. referred to as KCCQ-TSS in Module 4 A of the dossier
v. For the additionally presented endpoint cardiovascular mortality, an effect modification due to NYHA class (HR [95% CI]) is shown: NYHA II: 0.63 [0.49; 0.81]; NYHA III/IV 1.09 [0.85; 1.41]. See page 192 in the pharmaceutical company’s module 4A.

Abbreviations used:
AD: Absolute difference; eGFR: estimated glomerular filtration rate; EQ-5D: European Quality of Life Questionnaire - 5 Dimensions; ESRD: End-stage renal disease; HR: Hazard ratio; CI: Confidence interval; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: Mean difference; MMRM: mixed model for repeated measures; MV: mean value; n: number of patients with (at least 1) event; N: Number of patients evaluated; NYHA: New York Heart Association; OSS: Overall Summary Score; PGIC: Patient’s Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: preferred term; RCT: randomised controlled trial; VAS: visual analogue scale; RR: relative risk; SD: Standard deviation; SE: standard error; SOC: System organ class; TSS: Total Symptom Score; SAE: serious adverse event; AE: adverse event; vs: versus

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 forxiga (active ingredient: dapagliflozin) at the following publicly accessible link (last access: 23 April 2021):
https://www.ema.europa.eu/documents/product-information/forxiga-epar-product-information_de.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:	
Dapagliflozin	€ 583.66
+ optimised standard therapy	varies from patient to patient
Appropriate comparator therapy:	
optimised standard treatment	varies from patient to patient

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

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the G-BA website on 20 May 2021.

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

Berlin, 20 May 2021

Federal Joint Committee in accordance with Section 91 SGB V The chairman

Prof. Hecken