Dapagliflozin (new therapeutic indication: chronic kidney disease)

Resolution of: 17 February 2022 Valid until: unlimited
Entry into force on: 17 February 2022
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New therapeutic indication (according to the marketing authorisation of 5 August 2021):

Forxiga is indicated in adults for the treatment of chronic kidney disease.

Therapeutic indication of the resolution (resolution of 17 February 2022):

See new therapeutic indication according to marketing authorisation.

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

a) Adults with chronic kidney disease without symptomatic chronic heart failure as a comorbidity

Appropriate comparator therapy:

An optimised standard therapy for the treatment of chronic kidney disease, taking into account the underlying disease and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia)

Extent and probability of the additional benefit of dapagliflozin compared to optimised standard therapy for chronic kidney disease:

Hint of a considerable additional benefit

b) Adults with chronic kidney disease with additional symptomatic, chronic heart failure as a comorbidity

Appropriate comparator therapy:

An optimised standard therapy for the treatment of chronic kidney disease, taking into account the underlying disease and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia)

Extent and probability of the additional benefit of Dapagliflozin compared to optimised standard therapy for chronic kidney disease:

Hint for a minor additional benefit

Study results according to endpoints:[1]

a) Adults with chronic kidney disease without symptomatic chronic heart failure as a comorbidity

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall mortality
Morbidity	↑	Advantages in ESRD and total hospitalisation
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↑	Advantages with SAEs as well as in detail with 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

DAPA-CKD 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	2152	n.d. 101 (4.7)	2152	n.d. 146 (6.8)	0.69 [0.53; 0.89]; 0.003 AD = 2.1%

[1] Data from the dossier assessment of the IQWiG (A21-109) and from the addendum (A22-02), unless otherwise indicated.
[2] patient-individual standard therapy according to local guidelines for the treatment of both kidney disease and other comorbidities such as cardiovascular disease or type 2 diabetes mellitus

Morbidity

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)
Renal morbidity (combined endpoint)[c] *(presented additionally)*	2152	n.d. 142 (6.6)	2152	n.d. 243 (11.3)	0.56 [0.45; 0.68] < 0.001 AD = 4.7%
Confirms sustained reduction of eGFR by ≥ 50% *(presented additionally)*	2152	n.d. 112 (5.2)	2152	n.d. 201 (9.3)	0.53 [0.42; 0.67] < 0.001 AD = 4.1%
Renal death[d] *(presented additionally)*	2152	n.d. 2 (0.1)	2152	n.d. 6 (0.3)	0.34 [0.07; 1.70] 0.170
ESRD[b]	2152	n.d. 109 (5.1)	2152	n.d. 161 (7.5)	0.64 [0.51; 0.82] < 0.001 AD = 2.4%
Confirms sustained eGFR of < 15 ml/min/1.73 m^2	2152	n.d. 84 (3.9)	2152	n.d. 120 (5.6)	0.67 [0.51; 0.88] 0.004 AD = 1.7%
Chronic dialysis treatment	2152	n.d. 68 (3.2)	2152	n.d. 99 (4.6)	0.66 [0.49; 0.90] 0.008 AD = 1.4%
Receiving a kidney transplant	2152	n.d. 3 (0.1)	2152	n.d. 8 (0.4)	0.35 [0.09; 1.32] 0.105
Total hospitalisations	2152	n.d. 567 (26.3)	2152	n.d. 664 (30.9)	0.83 [0.74; 0.93] 0.001
Myocardial infarction[e]	2152	n.d. 40 (1.9)	2152	n.d. 37 (1.7)	1.07 [0.69; 1.68] 0.761
Stroke[e]	2152	n.d. 43 (2.0)	2152	n.d. 43 (2.0)	0.99 [0.65; 1.51] 0.967

Endpoint	Dapagliflozin + 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 Absolute difference (AD)
Health status (EQ-5D VAS)[f]	2152	523 (24.3)	2152	595 (27.6)	0.88 [0.79; 0.97]; 0.012[g] AD = 3.3%

Health-related quality of life

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 Absolute difference (AD)
KDQOL-36					
PCS	2152	509 (23.7)	2152	535 (24.9)	0.95 [0.86; 1.06] 0.355
MCS	2152	538 (25.0)	2152	564 (26.2)	0.95 [0.86; 1.06] 0.364
Burden of kidney disease	2152	613 (28.5)	2152	598 (27.8)	1.03 [0.93; 1.13] 0.611
Symptoms / problems of kidney disease	2152	307 (14.3)	2152	352 (16.4)	0.87 [0.76; 1.00] 0.057
Effects of kidney disease on daily life	2152	367 (17.1)	2152	422 (19.6)	0.87 [0.77; 0.99] 0.030

Side effects

Endpoint	Dapagliflozin + 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 Absolute difference (AD)
AE	Endpoint not assessed[h]				
SAE[m]	2149	550 (25.6)	2149	631 (29.4)	0.87 [0.79; 0.96] 0.006 AD = 3.8%
Discontinuation due to AEs[m]	2149	99 (4.6)	2149	93 (4.3)	1.07 [0.81; 1.40] 0.658
Specific adverse events					
Genital infections (AEs)	No usable data available				
Urinary tract infection (PT, AEs)	No usable data available				
Diabetic ketoacidosis (PT, AEs)[i]	2149	0 (0)	2149	2 (0.1)	0.20 [0.01; 4.16][j]; 0.212[k]
Pneumonia (PT, SAEs)	2149	44 (2.0)	2149	70 (3.3)	0.63 [0.43; 0.91]; 0.014[k]
Metabolism and nutrition disorders (SOC, SAEs)	2149	49 (2.3)	2149	84 (3.9)	0.58 [0.41; 0.83]; 0.002[k]

a. HR, CI and p value: Cox proportional hazards model with randomisation strata T2DM at baseline (yes vs no) and UACR (≤ 1000 mg/g vs > 1000 mg/g) as factors and baseline eGFR as covariate
b. Defined as confirmed sustained eGFR < 15 ml/min/1.73 m^2 or chronic dialysis treatment or receiving a kidney transplant
c. The combined endpoint includes confirmed sustained eGFR reduction of ≥ 50%, ESRD and renal death.
d. Deaths due to unexplained causes were counted as cardiovascular deaths in both studies, but not as renal deaths.
e. Fatal and non-fatal events
f. Percentage of patients with a decrease in score by ≥ 15 points compared to the start of the study, with a scale range of 0 to 100. Lower (decreasing) values mean a deterioration of symptomatology.
g. Effect estimate and p value from its logistic regression, adjusted with respect to the baseline
h. Only non-serious AEs that led to therapy discontinuation or dose adjustment or belonged to a selection of AEs predefined by the pharmaceutical company were recorded.
i. Probable and definite diabetic ketoacidosis adjudicated by an endpoint committee were analysed
j. The correction factor of 0.5 was used to calculate the effect estimators due to 0 events in 1 study arm.
k. Own calculation, unconditional exact test (CSZ method)
l. Percentage of patients who progressed to CKD stage 4 (eGFR of 15-29 ml/min/1.73 m^2) during the study and had an eGFR ≥ 40 ml/min/1.73 m^2 at randomisation.
m. Excluding disease-related events in SOC renal and urinary disorders and SOC cardiac disorders

Abbreviations used:
AD = absolute difference; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio; n.d. = no data; KDQOL = Kidney Disease Quality Of Life; CI = confidence interval; MCS = mental subscale; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculated; PCS = physical subscale; PT = preferred term; RR = relative risk; SOC = system organ class; SAE = serious adverse event; T2DM = type 2 diabetes mellitus; UACR = urine albumin-to-creatinine ratio; AE = adverse event; VAS = visual analogue scale; vs = versus

b) Adults with chronic kidney disease with additional symptomatic, chronic heart failure as a comorbidity

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No statistically significant or relevant difference.
Morbidity	↑	Advantage for total hospitalisation.
Health-related quality of life	∅	No data available.
Side effects	↑	Advantages with SAEs as well as in detail with specific AEs.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
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↔: no statistically significant or relevant difference
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n.a.: not assessable

DAPA-HF study: Dapagliflozin vs Placebo (each in addition to optimised standard therapy[3]), relevant sub-population: subjects with CKD[4]

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	962	n.d. 143 (14.9)	964	n.d. 168 (17.4)	0.85 [0.68; 1.07]; 0.162

[3] patient-individual 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)
[4] CKD sub-population of patients with an eGFR < 60 ml/min/1.73 m^2

Morbidity

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)
Renal morbidity (combined endpoint)[c] *(presented additionally)*	962	n.d. 18 (1.9)	964	n.d. 19 (2.0)	0.96 [0.50; 1.82] 0.893
Confirms sustained reduction of eGFR by ≥ 50% *(presented additionally)*	962	n.d. 7 (0.7)	964	n.d. 10 (1.0)	0.70 [0.27; 1.85] 0.476
Renal death[d] *(presented additionally)*	962	n.d. 0 (0)	964	n.d. 1 (0.1)	n.c.
ESRD[b]	962	n.d. 13 (1.4)	964	n.d. 8 (0.8)	1.64 [0.68; 3.97] 0.264
Confirms sustained eGFR of < 15 ml/min/1.73 m^2	962	n.d. 1 (0.1)	964	n.d. 0 (0)	n.c.
Chronic dialysis treatment	962	n.d. 13 (1.4)	964	n.d. 8 (0.8)	1.64 [0.68; 3.96] 0.265
Receiving a kidney transplant	962	n.d. 0 (0)	964	n.d. 0 (0)	–
Myocardial infarction[e]	962	n.d. 22 (2.3)	964	n.d. 21 (2.2)	1.06 [0.58; 1.93] 0.842
Stroke[e]	962	n.d. 22 (2.3)	964	n.d. 23 (2.4)	0.95 [0.53; 1.70] 0.860
Endpoint	**Dapagliflozin + 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 Absolute difference (AD)
Health status (EQ-5D VAS)[f]	845	241 (28.5)	835	218 (26.1)	1.09 [0.93; 1.28] 0.267
Total hospitalisations	960	367 (38.2)	962	440 (45.7)	0.84

					[0.75; 0.93] < 0.001 AD = 7.5%

Health-related quality of life

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 Absolute difference (AD)
KCCQ	No relevant data reported for sub-population.				

Side effects

Endpoint	Dapagliflozin + 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 Absolute difference (AD)
AE	Endpoint not assessed[g]				
SAE[j]	960	277 (28.9)	962	322 (33.5)	0.86 [0.75; 0.99] 0.029 AD = 4.6%
Discontinuation due to AEs[j]	960	36 (3.8)	962	30 (3.1)	1.20 [0.75; 1.94] 0.447
Specific adverse events					
Genital infections (AEs)	No usable data available				
Urinary tract infection (PT, AEs)	No usable data available				
Diabetic ketoacidosis (AEs)[h]	960	0 (0)	962	0 (0)	–
Non-cardiac chest pain (PT, SAEs)	960	1 (0.1)	962	10 (1.0)	0.10 [0.01; 0.78]; 0.007[i]
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	960	22 (2.3)	962	53 (5.5)	0.42 [0.26; 0.68]; < 0.001[i]

a. HR, CI and p value: Cox proportional hazards model taking into account the treatment arm, stratified by T2DM at randomisation (yes vs no) and adjusted for eGFR at baseline

b. Defined as confirmed sustained eGFR < 15 ml/min/1.73 m^2 or chronic dialysis treatment or receiving a kidney transplant
c. The combined endpoint includes confirmed sustained eGFR reduction of ≥ 50%, ESRD and renal death.
d. Deaths due to unexplained causes were counted as cardiovascular deaths in both studies, but not as renal deaths.
e. Fatal and non-fatal events
f. Percentage of patients with an increase in score by ≥ 15 points compared to the start of the study, with a scale range of 0 to 100. Higher (increasing) values mean an improvement of symptomatology
g. Only non-serious AEs that led to therapy discontinuation or dose adjustment or belonged to a selection of AEs predefined by the pharmaceutical company were recorded
h. Probable and definite diabetic ketoacidosis adjudicated by an endpoint committee were analysed
i. Own calculation, unconditional exact test (CSZ method)
j. Excluding disease-related events in SOC renal and urinary disorders and SOC cardiac disorders

Abbreviations used:
AD = absolute difference; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio; n.d. = no data available; KDQOL = Kidney Disease Quality Of Life; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculated; PT = preferred term; RR = relative risk; SOC = system organ class; SAE = serious adverse event; T2DM = type 2 diabetes mellitus; AE = adverse event; type 2; VAS = visual analogue scale; vs = versus

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

a) + b) Adults with chronic kidney disease

approx. 2,520,200 to 3,409,200 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 January 2022):

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

4. Treatment costs

Annual treatment costs:

a) Adults with chronic kidney disease without symptomatic chronic heart failure as a comorbidity

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Dapagliflozin	€ 584.56
+ 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 February 2022)

Costs for additionally required SHI services: not applicable

b) Adults with chronic kidney disease with additional symptomatic, chronic heart failure as a comorbidity

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Dapagliflozin	€ 584.56
+ 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 February 2022)

Costs for additionally required SHI services: not applicable