Resolution

Gemeinsamer Bundesausschuss

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: Type 1 diabetes mellitus)

of 17 October 2019

At its session on 17 October 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 21 June 2018:

Dapagliflozin

Resolution of: 17 October 2019
Entry into force on: 17 October 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 20 March 2019):

Forxiga is indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

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

Adult patients with insufficiently controlled type 1 diabetes mellitus and a BMI ≥ 27 kg/m^2 whose blood sugar is not adequately controlled despite optimal insulin therapy.

Appropriate comparator therapy:

Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin aspart, insulin glulisine, insulin lispro)[1]

Extent and probability of the additional benefit of dapagliflozin compared with the appropriate comparator therapy:

Hint for a minor additional benefit.

Study results by endpoints from the DEPICT 1 and DEPICT 2 studies for adult patients with insufficiently controlled type 1 diabetes mellitus and a BMI ≥ 27 kg/m^2 whose blood sugar is not adequately controlled despite optimal insulin therapy.

[1] The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus does not correspond to an appropriate comparator therapy if there is still the option of optimising insulin therapy.

Mortality

Endpoint category Endpoint Study	Dapagliflozin + insulin N	Dapagliflozin + insulin Patients with event n (%)	Placebo + insulin N	Placebo + insulin Patients with event n (%)	Dapagliflozin + insulin vs placebo + insulin RR [95% CI]; p value
Mortality					
Overall mortality					
DEPICT 1	159	0 (0)	154	0 (0)	–
DEPICT 2	127	0 (0)	135	0 (0)	–
Total					–

Morbidity, health-related quality of life

Endpoint category Endpoint Study	Dapagliflozin + insulin N[a]	Dapagliflozin + insulin Values at start of study MV (SD)	Dapagliflozin + insulin Change at the end of study MV[b] (SE)	Placebo + insulin N[a]	Placebo + insulin Values at start of study MV (SD)	Placebo + insulin Change at the end of study MV[b] (SE)	Dapagliflozin + insulin vs placebo + insulin MD [95% CI]; p value[b]
Morbidity							
Change of the HbA1c value[c]							
DEPICT 1	144	8.50 (0.67)	−0.34 (0.08)	153	8.42 (0.59)	0.08 (0.09)	−0.42 [−0.63; −0.22]; no data available
DEPICT 2	126	8.35 (0.58)	−0.13 (0.07)	133	8.37 (0.63)	0.11 (0.07)	−0.24 [−0.42; −0.06]; no data available
Total							−0.33 [−0.47; −0.19]; < 0.001
	N	**Patients with event n (%)**		**N**	**Patients with event n (%)**		**RR [95% CI]; p value**
HbA1c reduction ≥ 0.5 percentage points[c]							
DEPICT 1	145	65 (44.8)		153	38 (24.8)		1.80 [1.30; 2.51]; < 0.001
DEPICT 2	126	48 (38.1)		133	24 (18.0)		2.11 [1.38; 3.23]; < 0.001
Total[d]							1.92 [1.48; 2.50]; < 0.001

a: Number of patients included in the evaluation to calculate the effect estimate; values at the start of study may be based on other patient numbers.
b: MMRM with treatment, HbA1c baseline, week, stratum, treatment*week, HbA1c baseline*week; for pooled analysis, also the model terms study, treatment*study, week*study, and treatment*week*study
c: Sufficiently valid surrogate for microvascular sequelae
d: Own calculation, meta-analysis with fixed effect (Mantel-Haenszel)
HbA1c: Haemoglobin A1c; CI: Confidence Interval; MD: mean difference; MMRM: mixed model with repeated measurements; MV: mean value; n: number of patients with (at least 1) event; N: Number of patients evaluated; RCT: randomised controlled trial; RR: Relative Risk; SD: standard deviation; SE: Standard error; vs: versus

Endpoint category Endpoint Study	Dapagliflozin + insulin			Placebo + insulin			Dapagliflozin + insulin vs placebo + insulin
	N[a]	Values at start of study MV (SD)	Change at the end of study MV[b] (SE)	N[a]	Values at start of study MV (SD)	Change at the end of study MV[b] (SE)	MD [95% CI]; p value[b]
Morbidity							
EQ-5D VAS[c]							
DEPICT 1	143	76.50 (16.11)	3.84 (1.22)	144	76.42 (16.45)	1.25 (1.30)	2.59 [−0.33; 5.51]
DEPICT 2	118	65.21 (30.13)	10.76 (2.50)	116	69.89 (24.88)	4.11 (2.55)	6.64 [0.70; 12.59]
Total							4.87 [1.70; 8.04]; 0.003 Hedges' g [95% CI]: 0.24 [0.06; 0.42]
HFS-II (Worry Subscale)[d]							
DEPICT 1	Endpoint not recorded						
DEPICT 2	118	16.72 (11.89)	−0.24 (1.07)	115	16.52 (12.67)	−0.03 (1.11)	−0.21 [−2.72; 2.30]; 0.870
additionally shown:							
Body weight (kg)							
DEPICT 1	145	90.90 (17.36)	−3.05 (0.378)		94.05 (16.19)	0.02 (0.39)	−3.06 [−4.10; −2.02]; < 0.001
DEPICT 2	127	91.59 (14.13)	−3.83 (0.44)		91.57 (16.83)	0.92 (0.46)	−4.71 [−5.89; −3.51]; < 0.001
Total							−3.89 [−4.67; −3.11]; < 0.001
Health-related quality of life	Endpoint not recorded						

a: Number of patients included in the evaluation to calculate the effect estimate; values at the start of study may be based on other patient numbers.
b: MMRM with treatment, HbA1c baseline, week, stratum, treatment*week, HbA1c baseline*week; for pooled analysis, also the model terms study, treatment*study, week*study, and treatment*week*study
c: A positive change from start of study to end of study means an improvement; a positive effect estimate means an advantage for the intervention.
d: A positive change from the start of study to the end of study means a deterioration (greater anxiety of the patient with regard to hypoglycaemia); a negative effect estimate means an advantage for the intervention.
EQ-5D: European Quality of Life 5 Dimensions; HbA1c: Haemoglobin A1c; HFS-II: Hypoglycaemia Fear Survey II; CI: confidence interval; MMRM: mixed model with repeated measurements; MD: mean difference; MV: Mean Value; N: number of patients evaluated; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs: versus

Side effects

Endpoint category Endpoint Study	Dapagliflozin + insulin N	 Patients with event n (%)	Placebo + insulin N	 Patients with event n (%)	Dapagliflozin + insulin vs placebo + insulin RR [95% CI]; p value
Side effects					
AEs (additionally shown)					
DEPICT 1	*145*	*109 (75.2)*	*154*	*115 (74.7)*	–
DEPICT 2	*127*	*105 (82.7)*	*135*	*102 (75.6)*	–
SAEs					
DEPICT 1	145	17 (11.7)	154	16 (10.4)	1.13 [0.59; 2.15]; 0.775[a]
DEPICT 2	127	13 (10.2)	135	9 (6.7)	1.54 [0.68; 3.47]; 0.302
Total[b]					1.27 [0.77; 2.11]; 0.345
Discontinuation because of AEs					
DEPICT 1 (Sensitivity analysis[c)]	145	6 (4.1)	154	6 (3.9)	1.06 [0.35; 3.22]; 0.963[a]
DEPICT 2	127	11 (8.7)	135	7 (5.2)	1.67 [0.67; 4.18]; 0.272
Total[b] (Sensitivity analysis[c])					1.39 [0.69; 2.80]; 0.358
Symptomatic, confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dl)					
DEPICT 1	145	108 (74.5)	154	109 (70.8)	1.05 [0.92; 1.21]; 0.473
DEPICT 2	127	104 (81.9)	135	102 (75.6)	1.08 [0.96; 1.23]; 0.211
Total[d]					1.07 [0.97; 1.17]; 0.175
Symptomatic, confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dl)[g]					
DEPICT 1	159	128 (80.5)	154	114 (74.0)	1.09 [0.96; 1.23]; 0.074
DEPICT 2	127	112 (88.2)	135	110 (81.5)	1.08 [0.98; 1.20]; 0.131
Total[b]					1.09 [1.002; 1.18]; < 0.045
Symptomatic, confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dl)					
DEPICT 1 (Sensitivity analysis[c])	145	128 (88.3)	154	114 (74.0)	1.19 [1.07; 1.33]; 0.002[a]
DEPICT 2	127	112 (88.2)	135	110 (81.5)	1.08 [0.98; 1.20]; 0.131
Total[b] (Sensitivity analysis[c])					1.14 [1.06; 1.23]; < 0.001
Severe hypoglycaemias[e]					
DEPICT 1	145	4 (2.8)	154	2 (1.3)	2.12 [0.40; 11.42]; 0.380
DEPICT 2	127	2 (1.6)	135	2 (1.5)	1.06 [0.15; 7.43]; 0.951
Total[d]					1.59 [0.45; 5.59]; 0.466
DKAs (possible)					
DEPICT 1	145	0 (0.0)	154	1 (0.6)	0.35 [0.01; 8.62]; 0.524
DEPICT 2	127	5 (3.9)	135	1 (0.7)	5.31 [0.63; 44.87]; 0.125
Total[d]					2.66 [0.52; 13.58]; 0.241
DKAs (definitive)				no data available	
DKAs (possible + definitive)					
DEPICT 1	145	1 (0.7)	154	2 (1.3)	0.53 [0.05; 5.79]; 0.604
DEPICT 2	127	7 (5.5)	135	2 (1.5)	3.72 [0.79; 17.58]; 0.098
Total[d]					2.13 [0.65; 6.98]; 0.214

Endpoint category Endpoint Study	Dapagliflozin + insulin N	 Patients with event n (%)	Placebo + insulin N	 Patients with event n (%)	Dapagliflozin + insulin vs placebo + insulin RR [95% CI]; p value
Side effects					
Genital infections[f]					
DEPICT 1	145	24 (16.6)	154	6 (3.9)	4.25 [1.79; 10.09]; 0.001
DEPICT 2	127	15 (11.8)	135	6 (4.4)	2.66 [1.06; 6.64]; 0.036
Total[d]					3.45 [1.85; 6.45]; < 0.001
Gastrointestinal disorders (SOC) (AE)					
DEPICT 1	145	25 (17.2)	154	16 (10.4)	1.66 [0.92; 2.98]; 0.090
DEPICT 2	127	38 (29.9)	135	21 (15.6)	1.92 [1.20; 3.09]; 0.007
Total[b]					1.81 [1.251; 2.62]; 0.002
Urinary tract infections[f,g]					
DEPICT 1	159	16 (10.1)	154	10 (6.5)	1.55 [0.73; 3.31]; 0.258
DEPICT 2	127	16 (12.6)	135	10 (7.4)	1.70 [0.80; 3.61]; 0.166
Total[b]					1.62 [0.95; 2.77]; 0.075
Urinary tract infections[f]					
DEPICT 1 (Sensitivity analysis[c])	145	16 (11.0)	154	10 (6.5)	1.70 [0.80; 3.62]; 0.178[a]
DEPICT 2	127	16 (12.6)	135	10 (7.4)	1.70 [0.80; 3.61]; 0.166
Total[b] (Sensitivity analysis[c])					1.70 [1.00; 2.90]; 0.051

a: Own calculation: RR [95% CI] (asymptotic), unconditional exact test (CSZ method according to [6])
b: Own calculation, meta-analysis with fixed effect (Mantel/Haenszel)
c: Sensitivity analysis: assumption of 0 events for 14 incorrectly randomised patients in the dapagliflozin group (worst case analysis).
d: Pooled analysis
e: Symptomatic hypoglycaemia that has received medical treatment or has been treated with glucagon injections or intravenous glucose (regardless of blood glucose monitoring).
f: Collected via pre-specified PT list of the pharmaceutical company
g: Including incorrectly randomised patients

DKA: diabetic ketoacidosis; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; RCT: randomised controlled trial; RR: relative risk; SOC: System Organ Class; SAE: Serious Adverse Event; AE: Adverse Event; vs: versus

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

Adult patients with insufficiently controlled type 1 diabetes mellitus and a BMI ≥ 27 kg/m^2 and a GFR ≥ 60 ml/min whose blood sugar is not adequately controlled despite optimal insulin therapy:

Approx. 19,200 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: 10 September 2019):

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

Treatment with dapagliflozin may only be initiated and monitored by specialists who are experienced in the treatment of patients type 1 diabetes mellitus.

For patients in whom inadequate blood glucose control is associated with severe hypoglycaemia, particularly in the period prior to the planned start of dapagliflozin therapy, the indication for dapagliflozin should be carefully considered.

Before starting the treatment, it should be ensured that the ketone body levels are normal. During the first one to two weeks of treatment with dapagliflozin, the ketone bodies should be monitored regularly. Thereafter, the frequency of ketone body level testing should be individually adjusted according to the patient's lifestyle and/or risk factors.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide officially approved training material. The training material is intended to inform healthcare professionals and patients of the increased risk of ketoacidosis associated with dapagliflozin therapy.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Dapagliflozin	€ 445.30
Intensified conventional insulin therapy (ICT) Human insulin (NPH insulin) Human insulin (bolus insulin) Total:	 € 152.98 – € 458.95 € 152.98 – € 458.95 € 382.46 – € 764.92
Dapagliflozin + ICT:	€ 827.76 – € 1,210.22

Appropriate comparator therapy:	
<u>Intensified conventional insulin therapy (ICT)</u>	
Human insulin (NPH insulin)	€ 152.98 – € 458.95
Human insulin (bolus insulin)	€ 152.98 – € 458.95
Total:	€ 382.46 – € 764.92
Insulin detemir (monotherapy)	€ 635.27 – € 1,270.53
Insulin detemir	€ 254.11 – € 762.32
+ human insulin (bolus insulin)	€ 152.98 – € 458.95
Total:	€ 483.58 – € 1,068.29
Insulin glargine (monotherapy)	€ 542.15 – € 1,084.29
Insulin glargine	€ 216.86 – € 650.57
+ human insulin (bolus insulin)	€ 152.98 – € 458.95
Total:	€ 446.34 – € 956.54
Insulin aspart	€ 217.27 – € 651.81
+ human insulin (NPH insulin))	€ 152.98 – € 458.95
Total:	€ 446.75 – € 957.78
Insulin glulisine	€ 217.31 – € 651.92
+ human insulin (NPH insulin))	€ 152.98 – € 458.95
Total:	€ 446.79 – € 957.89
Insulin lispro	€ 187.27 – € 561.82
+ human insulin (NPH insulin))	€ 152.98 – € 458.95
Total:	€ 416.75 – € 867.79

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 October 2019

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/year
Medicinal product to be assessed:		
Intensified conventional insulin therapy	Blood glucose test strips Lancets Disposable needles	€ 540.20 – € 810.30 € 29.93 – € 44.90 € 246.76 – € 308.43
Dapagliflozin	Ketone test strips	Non-quantifiable
Appropriate comparator therapy		
Intensified conventional insulin therapy	Blood glucose test strips Lancets Disposable needles	€ 540.20 – € 810.30 € 29.93 – € 44.90 € 246.76 – € 308.43
Insulin detemir (monotherapy)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 61.69 – € 123.37
Insulin detemir + bolus insulin	Blood glucose test strips Lancets Disposable needles	€ 540.20 – € 810.30 € 29.93 – € 44.90 € 246.76 – € 308.43
Insulin glargine (monotherapy)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 61.69
Insulin glargine + bolus insulin	Blood glucose test strips Lancets Disposable needles	€ 540.20 – € 810.30 € 29.93 – € 44.90 € 246.76
Insulin aspart + NPH insulin	Blood glucose test strips Lancets Disposable needles	€ 540.20 – € 810.30 € 29.93 – € 44.90 € 246.76 – € 308.43

Designation of the therapy	Designation	Costs/year
Medicinal product to be assessed:		
Insulin glulisine + NPH insulin	Blood glucose test strips Lancets Disposable needles	€ 540.20 – € 810.30 € 29.93 – € 44.90 € 246.76 – € 308.43
Insulin lispro + NPH insulin	Blood glucose test strips Lancets Disposable needles	€ 540.20 – € 810.30 € 29.93 – € 44.90 € 246.76 – € 308.43

The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 17 October 2019.

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

Berlin, 17 October 2019

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

Prof Hecken