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 (Reassessment Because of New Scientific Knowledge (Type 2 Diabetes Mellitus))

of 19 December 2019

At its session on 19 December 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. Annex XII will be amended as follows:

1. The data concerning the active ingredient dapagliflozin as set out in the resolution of 6 June 2013 (BAnz AT 16 July 2013 B2) and the resolution of 21 June 2018 (BAnz AT 13 July 2018 B2) are hereby repealed.

2. Annex XII shall be amended in alphabetical order to include the active ingredient dapagliflozin as follows:

Dapagliflozin

Resolution of: 19 December 2019
Entry into force on: 19 December 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the product information of July 2019):

"Forxiga is indicated in adults for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1."

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

a) Adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance

a1) in patients without high cardiovascular risk[1]

Appropriate comparator therapy:

- Sulphonylurea (glibenclamide or glimepiride)

Extent and probability of the additional benefit of dapagliflozin as monotherapy compared with a sulphonylurea (glibenclamide or glimepiride):

An additional benefit is not proven.

a2) in patients at high cardiovascular risk[1] receiving further medication for the treatment of cardiovascular risk factors[2]

Appropriate comparator therapy:

- Sulphonylurea (glibenclamide or glimepiride)

Extent and probability of the additional benefit of dapagliflozin as monotherapy compared with a sulphonylurea (glibenclamide or glimepiride):

An additional benefit is not proven.

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar

[1] In the present case, high cardiovascular risk is defined according to the DECLARE-TIMI 58 Study (see study protocol, Wiviott et. al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380(4):347–357. DOI: 10.1056/NEJMoa1812389) and summarised here approximately as ≥ 40 years with at least one cardiovascular disease (ischaemic heart disease, cerebrovascular disease, or peripheral arterial occlusive disease) or women ≥ 60 years and men ≥ 55 years with at least one risk factor for cardiovascular disease (dyslipidemia, hypertension, current smoking with ≥ 5 cigarettes/day for at least one year at the time of randomisation)

[2] In particular anti-hypertensive agents, anticoagulants, and/or lipid-lowering agents

b1) in patients without high cardiovascular risk[1]

Appropriate comparator therapy:

- Metformin + sulphonylurea (glibenclamide or glimepiride) or
- Metformin + empagliflozin

Extent and probability of the additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy:

An additional benefit is not proven.

b2) in patients at high cardiovascular risk[1] receiving further medication for the treatment of cardiovascular risk factors[2]

Appropriate comparator therapy:

- Metformin + sulphonylurea (glibenclamide or glimepiride) or
- Metformin + empagliflozin or
- Metformin + liraglutide[3]

Extent and probability of the additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy:

Hint for a minor additional benefit

c) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

c1) in patients without high cardiovascular risk[1]

Appropriate comparator therapy:

- Human insulin + metformin or
- Only human insulin if metformin is intolerable or contraindicated in accordance with the product information or is not sufficiently effective because of advanced type 2 diabetes mellitus

Extent and probability of the additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy:

An additional benefit is not proven.

c2) in patients at high cardiovascular risk[1] receiving further medication for the treatment of cardiovascular risk factors[2]

Appropriate comparator therapy:

- Human insulin + metformin or
- Human insulin + empagliflozin[3] or
- Human insulin + liraglutide[3] or

[3] Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive agents, anticoagulants, and/or lipid-lowering agents (for the operationalisation, see study protocols: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–28. DOI 10.1056/NEJMoa1504720 or Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375: 311–322. DOI: 10.1056/NEJMoa1603827).

- Human insulin if the particular combination partners in accordance with the product information are incompatible or contraindicated or not sufficiently effective because of an advanced type 2 diabetes mellitus

Extent and probability of the additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy:

Hint for a minor additional benefit

d) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

d1) in patients without high cardiovascular risk[1]

Appropriate comparator therapy:

- The optimisation of the human insulin regime (possibly + metformin)

Extent and probability of the additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy:

An additional benefit is not proven.

d2) in patients at high cardiovascular risk[1] receiving further medication for the treatment of cardiovascular risk factors[2]

Appropriate comparator therapy:

- The optimisation of the human insulin regimen (possibly + metformin *or* empagliflozin[3] *or* liraglutide[3])

Extent and probability of the additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy:

Hint for a minor additional benefit

Study results by endpoints of the DECLARE-TIMI 58 Study for patient groups b2), c2), and d2) in adult patients with inadequately controlled diabetes mellitus and increased cardiovascular risk:

Endpoint category Endpoint	Intervention Dapagliflozin		Control Placebo		Intervention vs control
	N	Median time to event Patients with event n (%)	N	Median time to event Patients with event n (%)	HR [95% CI]; p value[a]
Mortality					
Overall mortality	8582	no data available 529 (6.2)	8578	no data available 570 (6.6)	0.93 [0.82; 1.04]; 0.198
Morbidity					
MACE					
Myocardial infarction[b, c, d]	8582	no data available 393 (4.6)	8578	no data available 441 (5.1)	0.89 [0.77; 1.01]; 0.080
fatal	8582	no data available 33 (0.4)	8578	no data available 40 (0.5)	0.82 [0.52; 1.30]; 0.400
non-fatal	8582	no data available 365 (4.3)	8578	no data available 404 (4.7)	0.90 [0.78; 1.03]; 0.136
ischaemic stroke[b, c, d]	8582	no data available 235 (2.7)	8578	no data available 231 (2.7)	1.01 [0.84; 1.21]; 0.916
fatal	8582	no data available 24 (0.3)	8578	no data available 17 (0.2)	1.41 [0.76; 2.62]; 0.283
non-fatal	8582	no data available 215 (2.5)	8578	no data available 214 (2.5)	1.00 [0.83; 1.21]; 0.978
stroke (fatal or non-fatal)[b, c, e]	8582	no data available 255 (3.0)	8578	no data available 263 (3.1)	0.96 [0.81; 1.14]; 0.659
haemorrhagic	8582	no data available 12 (0.1)	8578	no data available 26 (0.3)	no data available
of unknown aetiology	8582	no data available 13 (0.2)	8578	no data available 9 (0.1)	no data available
TIA[b]	8582	no data available 66 (0.8)	8578	no data available 51 (0.6)	no data available[f]

Cardiac failure					
Hospitalisation because of cardiac failure[b]	8582	no data available 212 (2.5)	8578	no data available 286 (3.3)	0.73 [0.61; 0.88]; < 0.001 *AD 0.8%*
severe cardiac failure (SMQ cardiac failure)	8582	no data available 410 (4.8)	8578	no data available 508 (5.9)	0.80 [0.70; 0.91]; < 0.001 *AD 1.1%*
Kidney disease[g]	8582	no data available 127 (1.5)	8578	no data available 238 (2.8)	0.53 [0.43; 0.66]; < 0.001 *AD 1.3%*
Confirmed sustained reduction in eGFR[h, i]	8582	no data available 120 (1.4)	8578	no data available 221 (2.6)	0.54 [0.43; 0.67]; < 0.001 *AD 1.2%*
End-stage kidney disease[h]	8582	no data available 6 (< 0.1)	8578	no data available 19 (0.2)	0.31 [0.13; 0.79]; 0.013 *AD approx. 0.1%*
Kidney transplant[h]	8582	no data available 0 (0)	8578	no data available 0 (0)	no data available
Dialysis ≥ 90 days[h]	8582	no data available 4 (< 0.1)	8578	no data available 16 (0.2)	no data available
confirmed sustained eGFR < 15 ml/min/1.73 m^2 [h]	8582	no data available 3 (< 0.1)	8578	no data available 4 (< 0.1)	no data available
Death because of kidney disease[h]	8582	no data available 6 (< 0.1)	8578	no data available 10 (0.1)	0.60 [0.22; 1.65]; 0.319
Treatment of retinopathy[j, k]	8582	no data available 102 (1.2)	8578	no data available 86 (1.0)	1.18 [0.89; 1.57]; 0.253
surgical or spontaneous non-surgical amputations	8574	no data available 120 (1.4)	8569	no data available 113 (1.3)	1.06 [0.82; 1.37]; 0.661
Health-related quality of life					
	Endpoint not recorded				

a: HR and CI from Cox proportional hazards model, stratified by cardiovascular risk and hematuria status at baseline, with treatment group as model term; p value from Wald test

b: Adjudicated by an endpoint committee (Clinical Events Committee)
c: Patients who have had multiple events are counted only once
d: The combined endpoint MACE also shows no statistically significant results
e: Ischaemic and haemorrhagic strokes as well as strokes with unclear aetiology
f: RR: 1.29 [0.90; 1.86]; 0.207. Effect, CI, and p value: unconditional exact test (CSZ method according to Andrés)
g: Combined endpoint consisting of the components: confirmed sustained ≥ 40% reduction of eGFR to eGFR < 60 ml/min/1.73 m^2 (using the CKD-EPI equation); end-stage kidney disease (consisting of the components: Dialysis ≥ 90 days, kidney transplant and/or confirmed sustained eGFR < 15 ml/min/1.73 m^2) and/or kidney death
h: All events in the entire course of the study and not the events included in the combined endpoint are presented
i: Comparable results to the endpoint doubling of serum creatinine levels accompanied by eGFR ≤ 45 ml/min/1.73 m^2 occur.
j: Consisting of the components: at least one laser treatment and/or intra-ocular treatment because of the progression and/or deterioration of diabetic retinopathy
k: There was no visual acuity assessment within the study.

Abbreviations:

AD: absolute difference; CKD-EPI: Chronic-Kidney-Disease-Epidemiology-Collaboration; eGFR: estimated glomerular filtration rate; HR: hazard ratio; CI: Confidence interval; MACE: major adverse cardiovascular event (cardiovascular death, myocardial infarction; stroke); n: number of patients with event: N: number of patients evaluated; SMQ: standardised MedDRA queries; TIA: transitory ischaemic attack

Endpoint category **Endpoint**	**Intervention** **Dapagliflozin**		**Control** **Placebo**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Side effects[b]					
Total rates					
AEs (additionally shown)	No usable data[c]				
SAE [d, k]	8574	2496 (29.1)	8569	2737 (31.9)	0.91 [0.87; 0.95]; < 0.001 *AD 2.8%*
Discontinuation because of AEs	8574	693 (8.1)	8569	592 (6.9)	1.17 [1.05; 1.30]; 0.004 *AD 1.2%*
Specific AE					
Hypoglycaemia (SAE)	8574	69 (0.8)	8569	86 (1.0)	0.80 [0.58; 1.10]; 0.207[e]
Bladder cancer[f, g] (AE)	8574	26 (0.3)	8569	45 (0.5)	0.58 [0.36; 0.93]; 0.026 *AD 0.2%*

Breast cancer[f, g] (AE)	8574	36 (0.4)	8569	35 (0.4)	1.03 [0.65; 1.64]; 0.907
Prostate carcinoma[f, g, h] (AEs)	5405	73 (1.4)	5323	63 (1.2)	1.14 [0.82; 1.60]; 0.440
DKAs[f, g] (all, AE)	no evaluations available				
definitive DKAs	8574	23 (0.3)	8569	11 (0.1)	2.09 [1.02; 4.28]; 0.040[e] *AD 0.2%*
probable DKAs	8574	9 (0.1)	8569	6 (< 0.1)	1.50 [0.53; 4.21]; 0.533[e]
possible DKAs	8574	6 (< 0.1)	8569	8 (< 0.1)	0.75 [0.26; 2.16]; 0.672[e]
Symptoms of a lack of volume[f] (AE)	8574	250 (2.9)	8569	256 (3.0)	0.98 [0.82; 1.16]; 0.846[e]

a: p value from Wald test
b: Side effects were monitored until the last round unless otherwise stated.
c: Not all AEs were fully documented in the study (only SAEs, discontinuations because of AEs, and AEs of special interest as per predefined PT collection).
d: Follow-up until the last round.
e: Effect, CI, and p value: unconditional exact test (CSZ method according to Andrés)
f: Collected via pre-defined PT collection of the pharmaceutical company
g: Adjudicated by an endpoint committee
h: Data related to male patients
i: Because the total proportion of the AE was not collected by the pharmaceutical company, the discontinuations because of this AE are used.
k: To the exclusion of subsequent complications: Death (including cardiovascular death), myocardial infarction, ischaemic stroke, hospitalisation because of cardiac failure, unstable angina pectoris, adjudicated revascularisation, renal events, and retinopathies

Abbreviations:

DKA: diabetic ketoacidosis; CI: confidence interval; n: number of patients with (at least one) event; N: number of patients evaluated; PT: preferred term; RR: relative risk; SAE: serious adverse event; AE: adverse event

Additionally presented endpoints of the DECLARE-TIMI 58 Study

	Intervention Dapagliflozin			Control Placebo			Intervention vs control
	N[a]	Values at start of study MV (SD)	Change at month 48 MV[b] (SE)	N[a]	Values at start of study MV (SD)	Change at month 48 MV[b] (SE)	MD [95% CI]; p value
Body weight [kg]	no data available	90.9 (20.2)	−3.5 (0.1)	no data available	90.6 (20.5)	−1.6 (0.1)	−1.93 [−2.13; −1.73]; < 0.001
HbA1c [%]	no data available	8.3 (1.2)	−0.4 (0.0)	no data available	8.3 (1.2)	−0.2 (0.0)	−0.24 [−0.28; −0.20]; < 0.001

a: The pharmaceutical company does not indicate how many patients were included in the analysis. At month 48, data for the endpoint body weight was collected from 71% of the patients; for the endpoint HbA1c, data was collected from 69% of the patients.
b: Calculation using a repeated measures model with treatment group, baseline, cardiovascular risk category, baseline hematuria status, rounds, and the interaction of rounds and treatment group as model terms. The pharmaceutical company does not specify the method of p value calculation.
Abbreviations:
HbA1c: Glycohaemoglobin; CI: confidence interval; MD: mean difference; MV: Mean Value; N: number of patients evaluated; RCT: randomised controlled study; SD: standard deviation

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

a) Adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance:

approx. 364,000 patients

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar

approx. 642,000 patients

c) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

approx. 440,000 patients

d) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

approx. 662,000 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: 13 November 2019):

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

4. Treatment costs

Annual treatment costs:

a) Adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance

a1) patients without high cardiovascular risk[1]

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Dapagliflozin	€ 359.45
Appropriate comparator therapy (sulphonylurea (glibenclamide or glimepiride)	
Glibenclamide or Glimepiride	€ 13.03 – € 78.17 € 29.67 – € 152.29

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

Costs for additionally required SHI services: not applicable

a2) patients at high cardiovascular risk[1] receiving further medication for the treatment of cardiovascular risk factors[2]

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Dapagliflozin	€ 359.45
Appropriate comparator therapy (sulphonylurea (glibenclamide or glimepiride)	
Glibenclamide or Glimepiride	€ 13.03 – € 78.17 € 29.67 – € 152.29

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

Costs for additionally required SHI services: not applicable

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar

b1) patients without high cardiovascular risk[1]

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be evaluated (dapagliflozin in combination with a hypoglycaemic agent[4] (except insulin))	
Dapagliflozin	€ 359.45
Metformin	€ 33.24 – € 99.71
Glibenclamide or Glimepiride	€ 13.03 – € 78.17 € 29.67 – € 152.29
Dapagliflozin + metformin *or* Dapagliflozin + glibenclamide *or* Dapagliflozin + glimepiride	Total: € 392.69 – € 459.16 € 372.48 – € 437.62 € 389.12–511.74
Appropriate comparator therapy	
Metformin	€ 33.24 – € 99.71
Sulphonylurea Glibenclamide or Glimepiride	 € 13.03 – € 78.17 € 29.67 – € 152.29
Empagliflozin	€ 658.93
Metformin + glibenclamide *or* metformin + glimepiride Metformin + empagliflozin	Total: € 46.26–177.88 € 62.90–251.99 € 692.17 – € 758.64

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

Costs for additionally required SHI services: not applicable

[4] An example of combination therapy with a hypoglycaemic agent is the combination with metformin or with a sulphonylurea (glibenclamide or glimepiride).

b2) patients at high cardiovascular risk[1] receiving further medication for the treatment of cardiovascular risk factors[2]

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be evaluated (dapagliflozin in combination with a hypoglycaemic agent[4] (except insulin))	
Dapagliflozin	€ 359.45
Metformin	€ 33.24 – € 99.71
Glibenclamide or Glimepiride	€ 13.03 – € 78.17 € 29.67 – € 152.29
Dapagliflozin + metformin *or* Dapagliflozin + glibenclamide *or* Dapagliflozin + glimepiride	Total: € 392.69 – € 459.16 € 372.48 – € 437.62 € 389.12–511.74
Appropriate comparator therapy	
Metformin	€ 33.24 – € 99.71
Sulphonylurea Glibenclamide or Glimepiride	 € 13.03 – € 78.17 € 29.67 – € 152.29
Empagliflozin	€ 658.93
Liraglutide[3]	€ 1,308.84 – € 1,963.26
Metformin + glibenclamide *or* metformin + glimepiride Metformin + empagliflozin Metformin + liraglutide[3]	Total: € 46.26–177.88 € 62.90–251.99 € 692.17 – € 758.64 € 1,342.08 – € 2,062.97

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

Costs for additionally required SHI services:

Appropriate comparator therapy		
Liraglutide[3]	Disposable needles	€ 61.69

c) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

c1) patients without high cardiovascular risk[1]

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be evaluated (dapagliflozin in combination with at least two hypoglycaemic agents[5] (except insulin))	
Dapagliflozin	€ 359.45
Metformin	€ 33.24 – € 99.71
Glibenclamide *or* Glimepiride	€ 13.03 – € 78.17 € 29.67 – € 152.29
Dapagliflozin + metformin + glibenclamide *or* Dapagliflozin + metformin + glimepiride	Total: € 405.71 – € 537.33 € 422.35 – € 611.44
Appropriate comparator therapy	
Metformin	€ 33.24 – € 99.71
Human insulin (NPH insulin)	€ 382.46 – € 764.92
Human insulin (NPH-insulin) + metformin	Total: € 415.70 – € 864.63
Possible treatment only with human insulin if metformin is intolerable or contraindicated in accordance with the product information or is not sufficiently effective because of advanced type 2 diabetes mellitus	
Conventional insulin therapy (premixed insulin)	€ 382.46 – € 764.92

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

Costs for additionally required SHI services:

[5] An example of combination therapy with other hypoglycaemic agents is the combination with metformin and with a sulphonylurea (glibenclamide or glimepiride)

Designation of the therapy	Designation	Costs/year
Appropriate comparator therapy		
Human insulin (NPH insulin) as well as conventional insulin therapy (premixed insulin)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 61.69 – € 123.37

c2) patients at high cardiovascular risk[1] receiving further medication for the treatment of cardiovascular risk factors[2]

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be evaluated (dapagliflozin in combination with at least two hypoglycaemic agents[5] (except insulin))	
Dapagliflozin	€ 359.45
Metformin	€ 33.24 – € 99.71
Glibenclamide *or* Glimepiride	€ 13.03 – € 78.17 € 29.67 – € 152.29
Dapagliflozin + metformin + glibenclamide *or* Dapagliflozin + metformin + glimepiride	Total: € 405.71 – € 537.33 € 422.35 – € 611.44
Appropriate comparator therapy	
Metformin	€ 33.24 – € 99.71
Empagliflozin[3]	€ 658.93
Liraglutide[3]	€ 1,308.84 – € 1,963.26
Human insulin (NPH insulin)	€ 382.46 – € 764.92
Human insulin (NPH-insulin) + metformin Human insulin (NPH insulin) + empagliflozin[3] Human insulin (NPH insulin) + liraglutide[3]	Total: € 415.70 – € 864.63 € 1,041.40 – € 1,423.86 € 1,691.30 – € 2,728.19
Possibly therapy only with human insulin if, in accordance with the product information, metformin and empagliflozin[3] and liraglutide[3] are incompatible or contraindicated or are not sufficiently effective because of an advanced type 2 diabetes mellitus	
Conventional insulin therapy (premixed insulin)	€ 382.46 – € 764.92

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

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/year
Appropriate comparator therapy		
Human insulin (NPH insulin) as well as conventional insulin therapy (premixed insulin)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 61.69 – € 123.37
Liraglutide[3]	Disposable needles	€ 61.69

d) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment <u>with insulin</u> (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

d1) patients without high cardiovascular risk[1]

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed (dapagliflozin/metformin in combination with insulin (with or without another hypoglycaemic agent[6]))	
Dapagliflozin	€ 359.45
Human insulin (NPH insulin)	€ 382.46 – € 764.92
Possibly metformin	€ 33.24 – € 99.71
Dapagliflozin + human insulin (NPH insulin) *or* Dapagliflozin + human insulin (NPH insulin) + metformin	Total: € 741.91 – € 1,124.37 € 775.15–1,224.08
Appropriate comparator therapy	
Metformin	€ 33.24 – € 99.71
<u>Conventional insulin therapy (premixed insulin)</u> <u>Conventional insulin therapy (premixed insulin) possibly + metformin</u> Conventional insulin therapy (premixed insulin) + metformin	€ 382.46 – € 764.92 Total: € 415.70 – € 864.63
<u>Intensified conventional insulin therapy</u>	

[6] For example, for the combination with another hypoglycaemic agent, metformin is stated

Designation of the therapy	Annual treatment costs per patient
Human insulin (NPH insulin) Human insulin (bolus insulin)	€ 152.98 – € 458.95 € 152.98 – €458.95 Total: € 382.46 – € 764.92

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

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/year
Medicinal product to be assessed (dapagliflozin/metformin in combination with insulin (with or without another hypoglycaemic agent))		
Human insulin (NPH insulin)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 61.69 – € 123.37
Appropriate comparator therapy		
Conventional insulin therapy (premixed insulin)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 61.69 – € 123.37
Intensified conventional insulin therapy	Blood glucose test strips Lancets Disposable needles	€ 540.20 – € 810.30 € 29.93 – € 44.90 € 246.74 – € 308.43

d2) patients at high cardiovascular risk[1] receiving further medication for the treatment of cardiovascular risk factors[2]

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed (dapagliflozin in combination with insulin (with or without another hypoglycaemic agent[6]))	
Dapagliflozin	€ 359.45
Human insulin (NPH insulin)	€ 382.46 – € 764.92
Possibly metformin	€ 33.24 – € 99.71
Dapagliflozin + human insulin (NPH insulin) *or*	Total: € 741.91 – € 1,124.37

Designation of the therapy	Annual treatment costs per patient
Dapagliflozin + human insulin (NPH insulin) + metformin	€ 775.15–1,224.08
Appropriate comparator therapy	
Metformin	€ 33.24 – € 99.71
Empagliflozin[3]	€ 658.93
Liraglutide[3]	€ 1,308.84 – € 1,963.26
Conventional insulin therapy (premixed insulin) Conventional insulin therapy (premixed insulin) possibly + metformin *or* empagliflozin[3] *or* liraglutide[3] Conventional insulin therapy (premixed insulin) + metformin Conventional insulin therapy (premixed insulin) + empagliflozin[3] Conventional insulin therapy (premixed insulin) + liraglutide[3]	€ 382.46 – € 764.92 Total: € 415.70 – € 864.63 € 1,041.40 – € 1,423.86 € 1,691.30 – € 2,728.19
Intensified conventional insulin therapy Human insulin (NPH insulin) Human insulin (bolus insulin) Total:	 € 152.98 – € 458.95 € 152.98 – €458.95 Total: € 382.46 – € 764.92

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

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/year
Medicinal product to be assessed (dapagliflozin/metformin in combination with insulin (with or without another hypoglycaemic agent))		
Human insulin (NPH insulin)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 61.69 – € 123.37
Appropriate comparator therapy		
Conventional insulin therapy (premixed insulin)	Blood glucose test strips Lancets Disposable needles	€ 135.05 – € 405.15 € 7.48 – € 22.45 € 61.69 – € 123.37

Designation of the therapy	Designation	Costs/year
Intensified conventional insulin therapy	Blood glucose test strips Lancets Disposable needles	€ 540.20 – € 810.30 € 29.93 – € 44.90 € 246.74 – € 308.43
Liraglutide[3]	Disposable needles	€ 61.69

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 19 December 2019.

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

Berlin, 19 December 2019

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

Prof. Hecken