**Dapagliflozin/Metformin** (Reassessment Because of New Scientific Knowledge (Type 2 Diabetes Mellitus))

| | | |
|---|---|---|
| Resolution of: | 19 December 2019 | Valid until: unlimited |
| Entry into force on: | 19 December 2019 | |
| Federal Gazette, BAnz AT 27 01 2020 B2 | | |

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

Xigduo is indicated in adults for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise:

– in patients insufficiently controlled on their maximally tolerated dose of metformin alone
– in combination with other medicinal products for the treatment of diabetes in patients insufficiently controlled with metformin and these medicinal products
– in patients already being treated with the combination of dapagliflozin and metformin as separate tablets

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.

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

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a) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment <u>with one</u> other hypoglycaemic agent (apart from insulin, here metformin) do not sufficiently control the blood sugar

a1) 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/metformin compared with the appropriate comparator therapy:**

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:**

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[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

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

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

Hint for a minor additional benefit


b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment <u>with at least two</u> hypoglycaemic agents (including metformin, apart from insulin) do not sufficiently control the blood sugar

   b1)  in patients without high cardiovascular risk[1]

   **Appropriate comparator therapy:**
   - Human insulin + metformin

   **Extent and probability of the additional benefit of dapagliflozin/metformin 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:**
   - Human insulin + metformin or
   - Human insulin + empagliflozin[3] or
   - Human insulin + liraglutide[3] or
   - 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/metformin compared with the appropriate comparator therapy:**

   Hint for a minor additional benefit


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

   c1)  in patients without high cardiovascular risk[1]

   **Appropriate comparator therapy:**
   - The optimisation of the human insulin regime (possibly + metformin)

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[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).

2

**Extent and probability of the additional benefit of dapagliflozin/metformin 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:**

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

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

Hint for a minor additional benefit

**Study results by endpoints[4] of the DECLARE-TIMI 58 Study for patient groups a), b), and c) in adult patients with inadequately controlled diabetes mellitus and increased cardiovascular risk (sub-population at least 1700 mg of metformin at start of study):**

| Endpoint category Endpoint | Intervention Dapagliflozin + metformin | | Control Placebo + metformin | | 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 | 4627 | no data available 244 (5.3) | 4691 | no data available 267 (5.7) | 0.93 [0.78; 1.11]; 0.410 |
| **Morbidity** | | | | | |
| MACE | | | | | |
| Myocardial infarction[b, c, d] | 4627 | no data available 208 (4.5) | 4691 | no data available 253 (5.4) | 0.83 [0.69; 1.00]; 0.051 |
| fatal | 4627 | no data available 12 (0.3) | 4691 | no data available 23 (0.5) | 0.53 [0.26; 1.06]; 0.073 |
| non-fatal | 4627 | no data available 197 (4.3) | 4691 | no data available 233 (5.0) | 0.86 [0.71; 1.04]; 0.112 |
| ischaemic stroke[b, c, d] | 4627 | no data available 130 (2.8) | 4691 | no data available 110 (2.3) | 1.20 [0.93; 1.54]; 0.163 |
| fatal | 4627 | no data available 15 (0.3) | 4691 | no data available 8 (0.2) | 1.90 [0.81; 4.49]; 0.142 |
| non-fatal | 4627 | no data available 117 (2.5) | 4691 | no data available 102 (2.2) | 1.16 [0.89; 1.52]; 0.265 |
| stroke (fatal or non-fatal)[b, c, e] | 4627 | no data available 138 (3.0) | 4691 | no data available 129 (2.7) | no data available[f] |
| haemorrhagic | | no data available | | no data available | no data available |

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4 Data from the dossier evaluation of the IQWiG (A19-52) of 27 September 2019 unless otherwise indicated.

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|---|---|---|---|---|---|
| of unknown aetiology | | no data available | | no data available | no data available |
| TIA[b] | | no data available | | no data available | no data available |
| Cardiac failure | | | | | |
| Hospitalisation because of cardiac failure[b] | 4627 | no data available<br>84 (1.8) | 4691 | no data available<br>146 (3.1) | 0.58<br>[0.44; 0.76];<br>< 0.001<br>*AD 1.3%* |
| severe cardiac failure (SMQ cardiac failure) | 4627 | no data available<br>179 (3.9) | 4691 | no data available<br>264 (5.6) | 0.68<br>[0.56; 0.82];<br>< 0.001<br>*AD 1.7%* |
| Kidney disease[g] | 4627 | no data available<br>69 (1.5) | 4691 | no data available<br>145 (3.1) | 0.48<br>[0.36; 0.63];<br>< 0.001<br>*AD 1.6%* |
| Confirmed sustained reduction in eGFR[h, i] | 4627 | no data available<br>68 (1.5) | 4691 | no data available<br>140 (3.0) | 0.49<br>[0.36; 0.65];<br>< 0.001<br>*AD 1.5%* |
| End-stage kidney disease[h] | 4627 | no data available<br>1 (< 0.1) | 4691 | no data available<br>6 (0.1) | 0.17<br>[0.02; 1.42];<br>0.101 |
| Dialysis ≥ 90 days[h] | | no data available | | no data available | no data available |
| Kidney transplant[h] | | no data available | | no data available | no data available |
| confirmed sustained eGFR < 15 ml/min/1.73 $m^2$ [h] | | no data available | | no data available | no data available |
| Death because of kidney disease[h] | 4627 | no data available<br>1 (< 0.1) | 4691 | no data available<br>4 (< 0.1) | 0.25<br>[0.03; 2.24];<br>0.216 |
| Treatment of retinopathy[j, k] | 4627 | no data available<br>67 (1.4) | 4691 | no data available<br>49 (1.0) | no data available[l] |
| surgical or spontaneous non-surgical amputations | 4627 | no data available<br>59 (1.3) | 4691 | no data available<br>63 (1.3) | no data available[m] |
| **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

c: Patients who have had multiple events are counted only once

d: The combined endpoint MACE also shows no statistically significant results.

e: Information refers to ischaemic and haemorrhagic strokes as well as strokes with unclear aetiology

f: RR: 1.08 [0.86; 1.37]; p = 0.533. 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: Combined endpoint 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 is no visual acuity assessment within the study.

l: RR: 1.39 [0.96; 2.00]; p = 0.080; calculation of the pharmaceutical company, p value from Wald test

m: RR: 0.95 [0.67; 1.35]; p = 0.773; calculation of the pharmaceutical company, p value from Wald test

Abbreviations:

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); MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with event; N: number of patients evaluated; SMQ: standardised MedDRA queries; TIA: transitory ischaemic attack

| Endpoint category Endpoint | Intervention Dapagliflozin + metformin | | Control Placebo + metformin | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | RR [95% CI]; p value[a] |
| **Side effects[j]** | | | | | |
| Total rates | | | | | |
| AEs (additionally shown) | No usable data[b] | | | | |
| SAE (non-fatal, excluding subsequent complications)[f] | 4622 | 1263 (27.3) | 4689 | 1455 (31.0) | 0.88 [0.83; 0.94]; < 0.001 *AD 3.7%* |
| Discontinuation because of AE | 4622 | 310 (6.7) | 4689 | 301 (6.3) | 1.04 [0.90; 1.22]; 0.575 |
| Specific AE | | | | | |

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|---|---|---|---|---|---|
| Hypoglycaemia (PT, SAE) | 4622 | 32 (0.7) | 4689 | 48 (1.0) | 0.68 [0.43; 1.06] 0.084[g] |
| Bladder cancer[c, d] | 4622 | 12 (0.3) | 4689 | 25 (0.5) | 0.49 [0.24; 0.97]; 0.040 *AD 0.2%* |
| Breast cancer[c, d] | 4622 | 17 (0.4) | 4689 | 23 (0.5) | 0.75 [0.40; 1.40]; 0.367 |
| Prostate carcinoma[c, d, e] | 3048 | 36 (1.2) | 2994 | 31 (1.0) | 1.14 [0.71; 1.84]; 0.589 |
| DKAs[c, d] (all, AE) | no evaluations available | | | | |
| definitive DKAs | 4622 | 12 (0.3[i]) | 4689 | 6 (0.1[i]) | 2.03 [0.76; 5.40]; 0.153[g] |
| probable DKAs | 4622 | 3 (0.1[i]) | 4689 | 3 (0.1[i]) | 1.01 [0.20; 5.02]; > 0.999[g] |
| possible DKAs | no evaluations available | | | | |
| Symptoms of a lack of volume[c] (AE) | 4622 | 125 (2.7) | 4689 | 107 (2.3) | 1.19 [0.92; 1.53]; 0.192 |
| Respiratory, thoracic, and mediastinal disorders (SOC, SAE) | 4622 | 97 (2.1) | 4689 | 134 (2.9) | 0.73 [0.57; 0.95]; 0.019[g] *AD 0.8%* |
| Hepatobiliary disorders (SOC, SAE) | 4622 | 52 (1.1) | 4689 | 77 (1.6) | 0.69 [0.48; 0.97]; 0.033[g] *AD 0.5%* |

a: p value from Wald test

b: Not all AEs were fully documented in the study (only SAE, discontinuations because of AE, and AE of special interest as per predefined PT collection).

c: Collected via pre-defined PT collection of the pharmaceutical company

d: Adjudicated by an endpoint committee

e: Data related to male patients

f: 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

g: Calculation by the IQWiG, exact unconditional test (CSZ method according to Andrés

i: Calculation of the IQWiG

j: Follow-up until the last round

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; SOC: system organ class; SAE: serious adverse event; AE: adverse event

**Additionally presented endpoints of the DECLARE-TIMI 58 Study (sub-population, at least 1700 mg of metformin at the start of study)**

| | Intervention Dapagliflozin + metformin | | | Control Placebo + metformin | | | 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 | 93.0 (19.6) | −3.7 (0.1) | no data available | 92.1 (20.0) | −1.6 (0.1) | −2.04 [−2.25; −1.83]; < 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) | −0.25 [−0.31; −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 75% of the patients; for the endpoint HbA1c, data was collected from 73% 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 and the treatment with one other hypoglycaemic agent (apart from insulin, here metformin) do not sufficiently control the blood sugar

approx. 607,000 patients

b)  Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (including metformin, apart from insulin) do not sufficiently control the blood sugar
approx. 261,000 patients

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

approx. 271,000 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/metformin) at the following publicly accessible link (last access: 13 November 2019):

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

## 4. Treatment costs

**Annual treatment costs:**

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

a1) patients without high cardiovascular risk[1]

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Medicinal product to be assessed (dapagliflozin/metformin) | |
| Dapagliflozin/metformin[5] | € 359.45 |
| Appropriate comparator therapy | |
| Metformin | € 33.24 – € 99.71 |
| Sulphonylurea<br>  Glibenclamide or<br>  Glimepiride | <br>€ 13.03 – € 78.17<br>€ 29.67 – € 152.29 |
| Empagliflozin | € 658.93 |
| <br>Metformin + glibenclamide *or* metformin + glimepiride<br><br>Metformin + empagliflozin | Total:<br><br>€ 46.26–177.88<br>€ 62.90–251.99<br><br>€ 692.17 – € 758.64 |

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

a2) in 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/metformin) | |
| Dapagliflozin/metformin[5] | € 359.45 |
| Appropriate comparator therapy | |

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[5] Potencies available (dapagliflozin/metformin) 5/850 mg; 5/1000 mg.

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Metformin | € 33.24 – € 99.71 |
| Sulphonylurea<br><br>Glibenclamide or<br><br>Glimepiride | <br><br>€ 13.03 – € 78.17<br><br>€ 29.67 – € 152.29 |
| Empagliflozin | € 658.93 |
| Liraglutide[3] | € 1,308.84 – € 1,963.26 |
| <br><br>Metformin + glibenclamide *or* metformin + glimepiride<br><br>Metformin + empagliflozin<br><br>Metformin + liraglutide[1] | Total:<br><br>€ 46.26–177.88<br>€ 62.90–251.99<br><br>€ 692.17 – € 758.64<br><br>€ 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 |

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment <u>with at least two</u> hypoglycaemic agents (including metformin, apart from insulin) do not sufficiently control the blood sugar

b1) in patients without high cardiovascular risk[1]

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Medicinal product to be evaluated (dapagliflozin/metformin in combination with other hypoglycaemic agents[6] (except insulin)) | |
| Dapagliflozin/metformin[5] | € 359.45 |
| Glibenclamide or<br><br>Glimepiride | € 13.03 – € 78.17<br><br>€ 29.67 – € 152.29 |

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

10

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Dapagliflozin/metformin + glibenclamide *or*<br>Dapagliflozin/metformin + glimepiride | Total:<br>€ 372.48 – € 437.62<br>€ 389.12 – € 511.74 |
| Appropriate comparator therapy | |
| Metformin | € 33.24 – € 99.71 |
| Human insulin (NPH insulin) | € 382.46 – € 764.92 |
| Human insulin (NPH-insulin) + metformin | Total:<br>€ 415.70 – € 864.63 |
| Possibly therapy only with human insulin if, in accordance with the product information, metformin and empagliflozin[1] and liraglutide[1] 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<br>Lancets<br>Disposable needles | € 135.05 – € 405.15<br>€ 7.48 – € 22.45<br>€ 61.69 – € 123.37 |

b2) in patients at high cardiovascular risk[1] ~~in combination with~~ 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/metformin in combination with other hypoglycaemic agents[7] (except insulin)) | |
| Dapagliflozin/metformin[5] | € 359.45 |
| Glibenclamide *or*<br>Glimepiride | € 13.03 – € 78.17<br>€ 29.67 – € 152.29 |

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

11

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Dapagliflozin/metformin + glibenclamide *or* <br><br> Dapagliflozin/metformin + glimepiride | Total: <br> € 372.48 – € 437.62 <br> € 389.12 – € 511.74 |
| 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 <br><br> Human insulin (NPH insulin) + empagliflozin[3] <br> Human insulin (NPH insulin) + liraglutide[3] | Total: <br> € 415.70 – € 864.63 <br> € 1,041.40 – € 1,423.86 <br> € 1,691.30 – € 2,728.19 |
| Possibly therapy only with human insulin if, in accordance with the product information, metformin and empagliflozin[1] and liraglutide[1] 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 <br><br> Lancets <br><br> Disposable needles | € 135.05 – € 405.15 <br><br> € 7.48 – € 22.45 <br> € 61.69 – € 123.37 |
| Liraglutide[3] | Disposable needles | € 61.69 |

c) 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

c1) in patients without high cardiovascular risk[1]

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Medicinal product to be evaluated (dapagliflozin/metformin in combination with insulin) | |
| Dapagliflozin/metformin[5] | € 359.45 |
| Human insulin (NPH insulin) | € 382.46 – € 764.92 |
| Dapagliflozin/metformin + human insulin (NPH insulin) | Total: € 741.91 – € 1,124.37 |
| Appropriate comparator therapy | |
| Metformin | € 33.24 – € 99.71 |
| Conventional insulin therapy (premixed insulin)<br><br>Conventional insulin therapy (premixed insulin) possibly + metformin<br><br>Conventional insulin therapy (premixed insulin) + metformin | € 382.46 – € 764.92<br><br><br>Total:<br>€ 415.70 – € 864.63 |
| Intensified conventional insulin therapy<br>Human insulin (NPH insulin)<br>Human insulin (bolus insulin) | € 152.98 – € 458.95<br>€ 152.98 – €458.95<br>Total:<br>€ 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<br>Lancets<br>Disposable needles | € 135.05 – € 405.15<br>€ 7.48 – € 22.45<br>€ 61.69 – € 123.37 |
| Appropriate comparator therapy | | |
| Conventional insulin therapy (premixed insulin) | Blood glucose test strips | € 135.05 – € 405.15 |

| Designation of the therapy | Designation | Costs/year |
|---|---|---|
| | Lancets | € 7.48 – € 22.45 |
| | Disposable needles | € 61.69 – € 123.37 |
| Intensified conventional insulin therapy | Blood glucose test strips | € 540.20 – € 810.30 |
| | Lancets | € 29.93 – € 44.90 |
| | Disposable needles | € 246.74 – € 308.43 |

c2) in 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/metformin in combination with insulin)** | |
| Dapagliflozin/metformin[5] | € 359.45 |
| Human insulin (NPH insulin) | € 382.46 – € 764.92 |
| Dapagliflozin/metformin + human insulin (NPH insulin) | Total: <br> € 741.91 – € 1,124.37 |
| **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) | € 382.46 – € 764.92 |
| Conventional insulin therapy (premixed insulin) possibly + metformin *or* empagliflozin *or* liraglutide | |
| Conventional insulin therapy (premixed insulin) + metformin | Total: <br> € 415.70 – € 864.63 |
| Conventional insulin therapy (premixed insulin) + empagliflozin[3] | € 1.041.40 – € 1,423.86 |
| Conventional insulin therapy (premixed insulin) + liraglutide[3] | € 1,691.30 – € 2,728.19 |
| Intensified conventional insulin therapy | |

14

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Human insulin (NPH insulin) | € 152.98 – € 458.95 |
| Human insulin (bolus insulin) | € 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<br>Lancets<br>Disposable needles | € 135.05 – € 405.15<br>€ 7.48 – € 22.45<br>€ 61.69 – € 123.37 |
| Appropriate comparator therapy | | |
| Conventional insulin therapy (premixed insulin) | Blood glucose test strips<br>Lancets<br>Disposable needles | € 135.05 – € 405.15<br>€ 7.48 – € 22.45<br>€ 61.69 – € 123.37 |
| Intensified conventional insulin therapy | Blood glucose test strips<br>Lancets<br>Disposable needles | € 540.20 – € 810.30<br>€ 29.93 – € 44.90<br>€ 246.74 – € 308.43 |
| Liraglutide[3] | Disposable needles | € 61.69 |