# 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 Dulaglutide (Renewed Benefit Assessment Because of New Scientific Knowledge in Accordance with Section 13: Type 2 Diabetes Mellitus)

of 16 July 2020

In its session on 16 July 2020, 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 information relating to active ingredient dulaglutide as amended by the resolution of 16 July 2015 (Federal Gazette, BAnz AT 11 September 15 B1) is hereby repealed.
2. Annex XII shall be amended in alphabetical order to include the active ingredient dulaglutide as follows:

**Dulaglutide**

Resolution of: 16 July 2020
Entry into force on: 16 July 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

**Therapeutic indication (according to the product information last revised October 2019):**

Trulicity is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

– as monotherapy when metformin is considered inappropriate due to intolerance or contraindications

– in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, 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

**Appropriate comparator therapy:**

- Sulphonylurea (glibenclamide or glimepiride)

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

Additional benefit 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

**Appropriate comparator therapy:**

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

  liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents[1]

**Extent and probability of the additional benefit of dulaglutide in combination with other anti-diabetics compared with liraglutide:**

Additional benefit not proven

[1] for the operationalisation, see study protocol: Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375: 311–322. DOI: 10.1056/NEJMoa1603827

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

**Appropriate comparator therapy:**

- Human insulin + metformin or
- Human insulin + empagliflozin or
- Human insulin + liraglutide 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

  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 drugs, anticoagulants, and/or lipid-lowering agents[2]

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

Additional benefit not proven

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 renal insufficiency

**Appropriate comparator therapy:**

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

  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 drugs, anticoagulants, and/or lipid-lowering agents

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

Hint for a minor additional benefit.

d2) in patients with moderate or severe renal insufficiency in accordance with chronic kidney disease CKD stage 3 and 4 defined by an eGFR value < 60 to ≥ 15 ml/min/1.73 $m^2$

**Appropriate comparator therapy:**

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

  liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents[1]

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

[2] 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

Hint for a minor additional benefit.

**Study results according to endpoints[3]**

On 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

in patients with high cardiovascular risk

No data relevant for the benefit assessment were submitted.

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ Risk of bias | Summary |
|---|---|---|
| Mortality | ∅ | No data relevant for the benefit assessment were submitted. |
| Morbidity | ∅ | No data relevant for the benefit assessment were submitted. |
| Health-related quality of life | ∅ | No data submitted. |
| Side effects | ∅ | No data relevant for the benefit assessment were submitted. |

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

On: 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

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 and

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

each in patients with high cardiovascular risk

**REWIND study:**

| Endpoint category<br>Endpoint | Intervention<br>Dulaglutide | control<br>placebo | Intervention<br>vs control |
|---|---|---|---|

[3] Data from the dossier evaluation of the IQWiG (A20-09) of 29 April 2020 unless otherwise indicated.

| | N | Median time to event [95% CI] Patients with event n (%) | N | Median time to event [95% CI] Patients with event n (%) | HR [95% CI]; p value[a] |
|---|---|---|---|---|---|
| **Mortality** | | | | | |
| Overall mortality | 4949 | no data available 536 (10.8) | 4952 | no data available 592 (12.0) | 0.90 [0.80; 1.01]; 0.067 |
| **Morbidity** | | | | | |
| MACE[b] | 4949 | no data available 565 (11.4) | 4952 | no data available 642 (13.0) | 0.87 [0.77; 0.97]; 0.012 *AD 1.6%* |
| Cardiovascular death[c, d] | 4949 | no data available 317 (6.4) | 4952 | no data available 346 (7.0) | 0.91 [0.78; 1.06]; 0.211 |
| Non-lethal myocardial infarction[d, e] | 4949 | no data available 169 (3.4) | 4952 | no data available 188 (3.8) | 0.89 [0.72; 1.09]; 0.267 |
| Non-lethal stroke[d] | 4949 | no data available 135 (2.7) | 4952 | no data available 175 (3.5) | 0.76 [0.61; 0.95]; 0.017 *AD 0.8%* |
| Myocardial infarction | No usable data available[f] | | | | |
| lethal[d] | 4949 | no data available 26 (0.5) | 4952 | no data available 20 (0.4) | 1.29 [0.72; 2.30]; 0.397 |
| non-lethal[d] | 4949 | no data available 169 (3.4) | 4952 | no data available 188 (3.8) | 0.89 [0.72; 1.09]; 0.267 |
| Stroke[g] | 4949 | no data available 158 (3.2) | 4952 | no data available 205 (4.1) | 0.76 [0.62; 0.94]; 0.010 *AD 0.9%* |
| lethal[d] | 4949 | no data available 26 (0.5) | 4952 | no data available 33 (0.7) | 0.78 [0.47; 1.30]; 0.344 |
| non-lethal[d] | 4949 | no data available 135 (2.7) | 4952 | no data available 175 (3.5) | 0.76 [0.61; 0.95]; 0.017 *AD 0.8%* |
| Diabetic retinopathy | 4949 | no data available 95 (1.9) | 4952 | no data available 76 (1.5) | 1.24 [0.92; 1.68]; 0.156 |

| | | | | | |
|---|---|---|---|---|---|
| Diabetic retinopathy requiring laser therapy[d] | 4949 | no data available<br>53 (1.1) | 4952 | no data available<br>35 (0.7) | 1.51 [0.98; 2.31]; 0.059 |
| Diabetic retinopathy requiring laser vitrectromy[d] | 4949 | no data available<br>19 (0.4) | 4952 | no data available<br>13 (0.3) | 1.45 [0.72; 2.94]; 0.302 |
| Diabetic retinopathy requiring anti-VEGF therapy[d] | 4949 | no data available<br>50 (1.0) | 4952 | no data available<br>44 (0.9) | 1.13 [0.75; 1.69]; 0.561 |
| Chronic renal replacement therapy[h] | 4949 | no data available<br>16 (0.3) | 4952 | no data available<br>21 (0.4) | 0.75 [0.39; 1.44]; 0.393 |
| Persistent deterioration of renal function[i] | 4949 | no data available<br>34 (0.7) | 4952 | no data available<br>53 (1.1) | 0.63 [0.41; 0.97]; 0.037<br>*AD 0.4%* |
| Hospitalisation because of cardiac insufficiency[h] or urgent visit because of cardiac insufficiency | 4949 | no data available<br>213 (4.3) | 4952 | no data available<br>226 (4.6) | 0.93 [0.77; 1.12]; 0.456 |
| **Health-related quality of life** | | | | | |
| | No data available | | | | |
| **Side effects** | | | | | |
| Total rates | | | | | |
| AE (presented additionally) | 4949 | 4575 (92.4) | 4952 | 4535 (91.6) | - |
| SAE | 4949 | 1997 (40.4) | 4952 | 2056 (41.5) | RR[a] 0.97 [0.93; 1.02]; 0.249 |
| Discontinuation because of AE | 4949 | 434 (8.8) | 4952 | 298 (6.0) | RR[a] 1.46 [1.26; 1.68]; < 0.001<br>*AD 2.8%* |

| | | | | | |
|---|---|---|---|---|---|
| Specific AE | | | | | |
| Severe hypoglycaemias | 4949 | 57 (1.2) | 4952 | 63 (1.3) | RR[a] 0.91 [0.63; 1.29]; 0.681 |
| Acute pancreatitis[k] | 4949 | 23 (0.5) | 4952 | 13 (0.3) | RR[a] 1.75 [0.91; 3.36][l]; 0.098 |
| Gastrointestinal disorders (SOC, AE) | 4949 | 2346 (47.4) | 4952 | 1689 (34.1) | RR[a] 1.39 [1.32; 1.46]: < 0.001 *AD 13.1%* |
| Nausea (PT, AE) | 4949 | 737 (14.9) | 4952 | 271 (5.5) | RR[a] 2.72 [2.38; 3.11]; < 0.001 *AD 9.4%* |
| Diarrhoea (PT, AE) | 4949 | 671 (13.6) | 4952 | 442 (8.9) | RR[a] 1.52 [1.36; 1.70]; <0,001 *AD 4.7%* |

a: Calculation by the IQWiG, unconditional exact test (CSZ method)
c: combined cardiovascular endpoint without quiescent myocardial infarction
c. including deaths of unknown cause
d. All events in the entire course of the study and not the events included in the combined endpoint are presented.
e. Quiescent myocardial infarctions were not included in the analysis of non-lethal myocardial infarctions presented.
f. Quiescent myocardial infarctions were also included in the summary analysis of lethal and non-lethal myocardial infarctions. There are no evaluations without quiescent myocardial infarctions.
g. lethal and non-lethal; patients who had several strokes were counted only once
h. Dialysis or kidney transplantation
I. Persistent (in two consecutive measurements) doubling of the serum creatinine compared with baseline and persistent (in two consecutive calculations) eGFR ≤ 45 ml/min/1.73 m²
j. An urgent visit was defined as an urgent, unscheduled visit to a doctor or emergency room with clinical signs and symptoms of cardiac insufficiency and the need for additional or intensified therapy.
k: These are adjudicated events based on 2 of 3 of the following criteria: 1. Abdominal pain characteristic of acute pancreatitis, 2. ≥ 3-fold increase in the upper normal value limit of serum amylase and/or serum lipase, and 3. Detection by means of CT or MRI. discrepancies in Module 4 E; the events from the study report adjudicated by an independent, external, and blinded CEC are presented All events listed were symptomatic.
l. Peto-OR as estimator for the RR, IQWiG calculation

Abbreviations:

AD: absolute difference; CEC: clinical endpoint committee; CT: computed tomography; eGFR: estimated glomerular filtration rate; HR: hazard ratio; CI: confidence interval; MACE: major adverse cardiovascular event (cardiovascular death, myocardial infarction; stroke); MRI: magnetic resonance imaging; n: number of patients with (at least one): N: number of patients evaluated; PT: preferred term; RR: relative risk; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VEGF: vascular endothelial growth factor.

Supplementary presented endpoints of the REWIND study

| | Intervention Dulaglutide | | | control placebo | | | Intervention vs control |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at start of study MV (SD) | Change at month 60 MV[b] (SE) | N[a] | Values at start of study MV (SD) | Change at month 60 MV[b] (SE) | MD [95% CI]; p value[b] |
| HbA1c (%) | no data available | 7.3 (1.1) | −0.3 (0.02) | no data available | 7.4 (1.1) | 0.2 (0.02) | −0.51 [−0.57; -0.45]; < 0.001[c] |
| Body weight [kg] | no data available | 88.5 (18.4) | −3.5 (0.09) | no data available | 88.9 (18.6) | −2.2 (0.09) | −1.31 [−1.56; -1.07]; < 0.001 |

a: Number of patients who were taken into account in the evaluation for the calculation of the estimation of the effect; the values at the start of study can be based on other patient figures.
b: MMRM, adjusted for values at the start of study, rounds, interaction between treatment and rounds, and patient
Abbreviations:
HbA1c: glycohaemoglobin; CI: confidence interval; MD: Mean Difference; MMRM: mixed model with repeated measurements; MV: mean value; N: number of patients evaluated; SD: Standard Deviation; vs: versus

b) In 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 and with high cardiovascular risk[4]

**AWARD-6 study:**

| Endpoint category Endpoint | Intervention Dulaglutide + metformin | | | control Liraglutide + metformin | | | Intervention vs control |
|---|---|---|---|---|---|---|---|
| | N | Patients with event n (%) | | N | Patients with event n (%) | | RR [95% CI]; p value[a] |
| **Mortality** | | | | | | | |
| Overall mortality | 20 | (0) | | 24 | 0 (0) | | n.c. |
| | N[a] | Values at start of study MV (SD) | Change at the end of study MV (SE) | N[a] | Values at start of study MV (SD) | Change at the end of study MV (SE) | MD [95% CI]; p value |
| **Morbidity** | | | | | | | |
| Health status (EQ-5D-VAS) | No usable data available for the relevant sub-population[b] | | | | | | |
| **Health-related quality of life** | | | | | | | |
| | No data available[c] | | | | | | |

[4] in accordance with the inclusion criteria of the REWIND study

| Endpoint category<br>Endpoint | Intervention<br>Dulaglutide + metformin | | control<br>Liraglutide + metformin | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | RR [95% CI]; p value[a] |
| **Side effects** | | | | | |
| Total rates | | | | | |
| AEs (additionally shown) | 20 | 14 (70.0) | 24 | 12 (50.0) | - |
| SAE | 20 | 0 (0) | 24 | 2 (8.3) | 0.24 [0.01; 4.69]; 0.218 |
| Discontinuation because of AE | 20 | 0 (0) | 24 | 3 (12.5) | 0.17 [0.01; 3.11]; 0.119 |
| Specific AE | | | | | |
| Non-severe, symptomatic, confirmed hypoglycaemias | | | | | |
| PG ≤ 70 mg/dl | No usable data available for the relevant sub-population[b,d] | | | | |
| PG < 54 mg/dl | No usable data available for the relevant sub-population[b,d] | | | | |
| Severe hypoglycaemias | No usable data available for the relevant sub-population[b,d] | | | | |
| Acute pancreatitis[e] | 20 | 0 (0) | 24 | 0 (0) | n.c. |

a. IQWiG's calculation of RR, CI (asymptotic), and p value (unconditional exact test, CSZ method). In the case of 0 events in one study arm, the correction factor 0.5 was used to calculate effect and CI in both study arms.
b: In Module 4 B, for the relevant sub-population, only evaluations from which data that occurred after administration of an emergency medication were excluded are available. It was possible to administer emergency medication because of severe, persistent hyperglycaemia or as follow-up treatment after the end of the study medication.
c: The instruments APPADL and IW-SP surveyed for the endpoint category by the pharmaceutical company are assigned differently to the endpoint category morbidity. The associated endpoints are not included in the benefit assessment (see Section 2.8.3.4.3.2 of the IQWiG report).
d. In Module 4 B, only evaluations for the relevant sub-population in which hypoglycaemias that occurred after the administration of emergency medication were not considered are available. It was possible to administer emergency medication because of severe, persistent hyperglycaemia or as follow-up treatment after the end of the study medication.
e. Adjudicated events based on 2 of 3 of the following criteria: 1. Abdominal pain characteristic of acute pancreatitis, 2. 3-fold increase in serum amylase and/or serum lipase, and 3. CT or MRI results
Abbreviations:
APPADL: Ability to Perform Physical Activities of Daily Living; CT: computed tomography; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; IW-SP: Impact of Weight on Self-Perception; CI: confidence interval; MD: mean difference; MRI: magnetic resonance imaging; MV: mean value; N: Number of patients assessed; n.c: not calculable; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

On: 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

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ Risk of bias | Summary |
|---|---|---|
| Mortality | ↔ | There is no relevant difference for the benefit assessment |

| | | |
|---|---|---|
| Morbidity | ↔ | No more than negligible benefit for the endpoint “non-lethal stroke”, in the combined MACE endpoint, in particular in the single component non-lethal stroke, and in the endpoint “persistent deterioration of renal function” |
| Health-related quality of life | ∅ | No data submitted. |
| Side effects | ↓ | For the benefit assessment, there was a relevant disadvantage in the endpoint “discontinuation because of adverse events” and the endpoint “gastrointestinal disorders” |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |

On 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

**Summary of results for relevant clinical endpoints**

| **Endpoint category** | **Direction of effect/ Risk of bias** | **Summary** |
|---|---|---|
| Mortality | ↔ | There is no relevant difference for the benefit assessment |
| Morbidity | ↔ | No more than negligible benefit for the endpoint “non-lethal stroke”, in the combined MACE endpoint, in particular in the single component non-lethal stroke, and in the endpoint “persistent deterioration of renal function” |
| Health-related quality of life | ∅ | No data submitted. |
| Side effects | ↓ | For the benefit assessment, there was a relevant disadvantage in the endpoint “discontinuation because of adverse events” and the endpoint “gastrointestinal disorders” |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |

On 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 renal insufficiency

**AWARD-4 study[5]:**

| **Endpoint category**<br>Endpoint | **Intervention**<br>**Dulaglutide + insulin lispro ± metformin** | | **control**<br>**Insulin glargine + insulin lispro ± metformin** | | **Intervention vs control**<br>RR [95% CI] p value |
|---|---|---|---|---|---|
| | N | Patients with events n (%) | N | Patients with events n (%) | |
| **Mortality** | | | | | |
| Overall mortality | 295 | 1 (0.3)[c] | 296 | 3 (1.0)[c] | 0.37 [0.05; 2.62]; 0.624[a] |
| **Morbidity** | | | | | |
| Cardiovascular morbidity[c] | 295 | 5 (1.7) | 296 | 12 (4.1) | |
| | N[b] | Change at end of study MV[c] (SE) | N[b] | Change at end of study MV[c] (SE) | MD [95% CI] p value |
| Health status (EQ-5D VAS) | 279 | −0.46[e] (1.01) | 282 | −0.18[e] (1.01) | −0.28 [−3.08; 2.52][d] 0.815 |
| **Endpoints additionally shown** | | | | | |
| HbA1c changes[%] | 273 | −1.48 (0.08) | 276 | −1.23 (0.08) | −0.25 [−0.42; −0.07][d] 0.005 |
| Body weight [kg] | 225 | 0.34[f] (0.32) | 232 | 3.65[f] (0.31) | −3.31 [−4.17; −2.45] < 0.001 |
| **Health-related quality of life** | | | | | |
| No usable data are available. | | | | | |
| **Endpoint category**<br>Endpoint | **Intervention**<br>**Dulaglutide + insulin lispro ± metformin** | | **control**<br>**Insulin glargine + insulin lispro ± metformin** | | **Intervention vs control**<br>RR [95% CI] p value |
| | N | Patients with events n (%) | N | Patients with events n (%) | |
| **Side effects** | | | | | |
| AE | 295 | 223 (75.6) | 296 | 211 (71.3) | |
| SAE[g,h] | 295 | 27 (9.2) | 296 | 54 (18.2) | 0.50 [0.33; 0.77] |

[5] Data from the dossier evaluation of the IQWiG (A15-07) of 29 April 2015; RCT; AWARD-4 study; direct comparison: Dulaglutide + insulin lispro ± metformin vs insulin glargine + insulin lispro ± metformin.

| | | | | | |
|---|---|---|---|---|---|
| | | | | | 0.001 |
| Discontinuation because of AE[h,i] | 295 | 31 (10.5) | 296 | 9 (3.0) | 3.46 [1.67; 7.13][d]<br>< 0.001[k] |
| Severe hypoglycaemias[k] | No usable data are available. | | | | |
| symptomatic hypoglycaemia[l] (blood sugar < 54 mg/dl) | 295 | 198 (68.0) | 296 | 204 (69.2) | 0.98 [0.88; 1.10]<br>0.772 |
| symptomatic hypoglycaemia (blood sugar ≤ 70 mg/dl) | 295 | 237 (80.3) | 296 | 247 (83.4) | 0.96 [0.89; 1.04][d]<br>0.391[k] |
| Gastrointestinal disorders | 295 | 142 (48.1) | 296 | 54 (18.2) | 2.64 [2.02; 3.45][d]<br>< 0.001[k] |
| Nausea | 295 | 76 (25.8) | 296 | 10 (3.4) | 7.63 [4.02; 14.45][d]<br>< 0.001[k] |
| Diarrhoea | 295 | 50 (16.9) | 296 | 18 (6.1) | 2.79 [1.67; 4.66][d]<br>< 0.001[k] |
| Vomiting | 295 | 36 (12.2) | 296 | 5 (1.7) | 7.22 [2.88; 18.15][d]<br>< 0.001[k] |
| Dyspepsia | 295 | 27 (9.2) | 296 | 1 (0.3) | 27.09 [3.71; 198.07][d]<br>< 0.001[k] |
| Loss of appetite | 295 | 27 (9.2) | 296 | 0 (0) | 55.19 [3.38; 900.51][m]<br>< 0.001[k] |
| Pancreatitis | 295 | 0 (0) | 296 | 0 (0) | n.c. |
| Reaction at the injection site | 295 | 1 (0.3) | 296 | 0 (0.0) | 3.01 [0.12; 73.59][m]<br>0.349[k] |

a: Peto OR
b: Number of patients included in the evaluation to calculate the effect estimator; values at the start of study may be based on other patient numbers.
c: Data on cardiovascular morbidity as well as other micro- and macrovascular complications are not usable or not available for the assessment of an additional benefit.
For the endpoint cardiovascular morbidity, only the event rates are presented.
d: Own calculation of the IQWiG.
e: Endpoint change calculated using an ANCOVA model with LOCF for the difference in the changes from the start of study between treatment arms; adjusted for value at the start of study, country, and metformin treatment
f: MMRM evaluation of the ITT population.
g: Hypoglycaemia was also recorded. From the study documentation available, there is no indication that the result was different when events related to hypoglycaemia were included.
h: Results up to week 52.
i: Hypoglycaemia was also recorded. For the endpoint discontinuations because of AE, 0 vs 1 patients in the dulaglutide or insulin glargine treatment arm discontinued therapy because of hypoglycaemia. Deducting these patients with event yields the effect RR 3.89 [1.82; 8.32][f]; p = <0.001[g].
j: IQWiG's own calculation, unconditional exact test (CSZ method according to Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555–574).
k: It was not possible to derive results on severe hypoglycaemia from the operationalisations available.
l: Results up to week 52, not including observations after emergency medication.
m: Own calculation of the IQWiG, RR with correction factor of 0.5

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; CI: confidence interval; LOCF: Last Observation Carried Forward; MMRM: Mixed Models for Repeated Measurements; MV: mean value; MD: Mean difference, N: number of patients evaluated; n: number of patients with event; n.c.: not calculable; RCT:

randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; AE: adverse event; vs: versus

d1) in patients without renal insufficiency

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ Risk of bias | Summary |
|---|---|---|
| Mortality | ↔ | There is no relevant difference for the benefit assessment |
| Morbidity | ↔ | There is no relevant difference for the benefit assessment |
| Health-related quality of life | ∅ | No data submitted. |
| Side effects | ↑ | For the benefit assessment, there was a relevant advantage in the prevention of severe adverse events |

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

d2) in patients with moderate or severe renal insufficiency in accordance with chronic kidney disease CKD stage 3 and 4 defined by an eGFR value < 60 to ≥ 15 ml/min/1.73 $m^2$

**AWARD-7 study:**

| **Endpoint category**<br>**Endpoint** | **Intervention**<br>**Dulaglutide + insulin lispro** | | **control**<br>**Insulin glargine + insulin lispro** | | **Intervention vs control** |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | RR [95% CI]; p value[a] |
| **Mortality** | | | | | |
| Overall mortality | 192 | 3 (1.6) | 194 | 6 (3.1) | 0.50 [0.12; 2.04]; 0.324 |
| **Morbidity** | | | | | |
| Progression to end-stage renal disease (ESRD)[b] | 192 | 20 (10.4) | 194 | 27 (13.9) | 0.75 [0.43; 1.29]; 0.299[c] |
| **Health-related quality of life** | | | | | |
| | Endpoint not surveyed | | | | |
| **Side effects** | | | | | |
| Total rates | | | | | |
| AE (presented additionally) | 192 | 172 (89.6) | 194 | 160 (82.5) | – |
| SAE | 192 | 41 (21.4) | 194 | 56 (28.9) | 0.74 [0.52; 1.06]; 0.098 |
| Discontinuation because of AE | 192 | 22 (11.5)[d] | 194 | 7 (3.6) | 3.32 [1.45; 7.62]; 0.002 *AD 7.9%* |
| Specific AE | | | | | |
| Gastrointestinal disorders (SOC, AE) | 192 | 89 (46.4) | 194 | 46 (23.7) | 1.97 [1.47; 2.64]; < 0.001 *AD 22.7%* |
| Diarrhoea (PT, AE) | 192 | 33 (17.2) | 194 | 14 (7.2) | 2.39 [1.32; 4.30]; 0.003 *AD 10%* |
| Nausea (PT, AE) | 192 | 38 (19.8) | 194 | 9 (4.6) | 4.26 [2.12; 8.53]; < 0.001 *AD 15.2%* |

| | | | | | |
|---|---|---|---|---|---|
| Vomiting (PT, AE) | 192 | 26 (13.5) | 194 | 9 (4.6) | 2.93 [1.41; 6.05]; 0.002 *AD 8.9%* |
| Gastrointestinal disorders (SOC, AE) | 192 | 89 (46.4) | 194 | 46 (23.7) | 1.97 [1.47; 2.64]; < 0.001 *AD 22.7%* |
| Non-severe, symptomatic, confirmed hypoglycaemias | | | | | |
| PG ≤ 54 mg/dl | 190[e] | 58 (30.5) | 194 | 80 (41.2) | 0.74 [0.56; 0.97][c]; 0.029[c] *AD 10.7%* |
| PG < 70 mg/dl *presented additionally* | 190[e] | 88 (46.3) | 194 | 124 (63.9) | 0.72 [0.60; 0.87][c]; < 0.001[c] *AD 17.6%* |
| Severe hypoglycaemias[f] | 190[e] | 0 (0) | 194 | 12 (6.2) | 0.04 [0.00; 0.68][c]; < 0.001[c] *AD 6.2%* |
| Acute pancreatitis[g] | 192 | 2 (1.0) | 194 | 1 (0.5) | 1.98 [0.20; 19.10][h]; 0.601[c] |

a. RR, 95% CI, and p value Cochran-Mantel-Haenszel method stratified by CKD category at start of study
b. includes the following events: chronic renal disease stage V, need for renal replacement therapy or eGFR < 15 ml/min/1.73 m²
c. IQWiG's calculation of RR, CI (asymptotic), and p value (unconditional exact test (CSZ method)). In the case of 0 events in one study arm, the correction factor 0.5 was used to calculate effect and CI in both study arms.
d. Contain a "sudden death" event
e. No data on hypoglycaemia after the start of study were available for two patients in the dulaglutide treatment arm who dropped out of the study on the day of the start of study. As in the study report, they were excluded from the analysis of hypoglycaemia.
f. The present analysis of the endpoint does not consider events that occurred after the administration of an emergency medication or after the end of the study medication. However, the study documents show that this applies at most to one patient in the dulaglutide arm.
g. These are adjudicated events based on 2 of 3 of the following criteria: 1. Abdominal pain characteristic of acute pancreatitis, 2. ≥ 3-fold increase in the upper normal value limit of serum amylase and/or serum lipase, and 3. Detection by means of CT or MRI.
h. Peto-OR as estimator for the RR

Abbreviations

AD: absolute difference; CKD: chronic kidney disease; CT: computed tomography; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; CI: confidence interval; n: Number of patients with (at least one) event; MRI: magnetic resonance imaging; N: Number of patients evaluated; OR: Odds Ratio; PG: plasma glucose; PT: preferred term RCT: randomised controlled trial; RR: relative risk; SOC: system organ class; SAE: serious adverse event; AE: adverse event

Supplementary presented endpoints of the AWARD-7 study

| | Intervention Dulaglutide + insulin lispro | | | control Insulin glargine + insulin lispro | | | Intervention vs control |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at start of study MV (SD) | Change at end of study MV[b] (SE) | N[a] | Values at start of study MV (SD) | Change at end of study MV[b] (SE) | MD [95% CI]; p value[b] |
| HbA1c (%) | no data available | 8.60 (0.85) | −0.92 (0.12) | no data available | 8.56 (0.97) | −0.87 (0.12) | −0.05 [−0.28; 0.17]; no data available[c] |
| Body weight [kg] | no data available | 88.1 (16.01) | −2.27 (0.44)[d] | no data available | 88.2 (18.49) | 1.34 (0.43)[d] | −3.61 [−4.67; −2.55]; < 0.001[d] |
| BMI (kg/m²) | no data available | 32.1 (4.84) | −0.82 (0.16)[e] | no data available | 32.4 (5.33) | 0.54 (0.15)[e] | −1.37 [−1.75; −0.98]; < 0.001[e] |

a: Number of patients who were taken into account in the evaluation for the calculation of the estimation of the effect; the values at the start of study can be based on other patient figures.
b: Unless otherwise stated, MMRM evaluation of the mITT population adjusted for treatment, rounds, macroalbuminuria region, severity of chronic kidney disease at the start of study, HbA1c and logarithmic eGFR at the start of study, and interaction term for treatment and rounds
c. 1-sided p value based on tree gatekeeping method for adjustment for multiple testing (p = 0.314)
d. MMRM evaluation of the safety population; additionally adjusted for body weight at the start of study
e. MMRM evaluation of the safety population; additionally adjusted for BMI at the start of study

Abbreviations:

eGFR: estimated glomerular filtration rate; HbA1c: glycosylated haemoglobin; CI: confidence interval; MD mean difference; mITT: modified intention to treat; MMRM: mixed model with repeated measurements; MV: mean value; N: number of patients evaluated; SD: standard deviation; SE: Standard error

d2) in patients with moderate or severe renal insufficiency in accordance with chronic kidney disease CKD stage 3 and 4 defined by an eGFR value < 60 to ≥ 15 ml/min/1.73 m²

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ Risk of bias | Summary |
|---|---|---|
| Mortality | ↔ | There is no relevant difference for the benefit assessment |
| Morbidity | ↔ | There is no relevant difference for the benefit assessment |
| Health-related quality of life | ∅ | No data submitted. |
| Side effects | ↑ | For the benefit assessment, there was a relevant advantage in the prevention severe and non-severe symptomatic hypoglycaemias |

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

## 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 Trulicity® (active ingredient: dulaglutide at the following publicly accessible link (last access: 9 June 2020):

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

The use of GLP-1 receptor agonists (e.g. dulaglutide) was associated with a risk of developing acute pancreatitis. Patients should be informed about characteristic symptoms of acute pancreatitis, and the therapy should be changed if necessary.

## 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

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Medicinal product to be assessed | |
| Dulaglutide | € 1,243.63 |
| Appropriate comparator therapy (sulphonylurea (glibenclamide or glimepiride)) | |
| Glibenclamide or<br>Glimepiride | € 13.09 – 78.54<br>€ 29.79 – 152.41 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

**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

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Medicinal product to be evaluated (dulaglutide in combination with a hypoglycaemic agent[6] (except insulin)) | |
| Dulaglutide | € 1,243.63 |
| Metformin | € 33.36 – 100.07 |
| Glibenclamide or<br>Glimepiride | € 13.09 – 78.54<br>€ 29.79 – 152.41 |
| dulaglutide + metformin *or*<br>Dulaglutide + glibenclamide *or*<br>dulaglutide + glimepiride | Total:<br>€ 1,276.98 – 1,343.70<br>€ 1,256.72 – 1,322.16<br>€ 1,273.42 – 1,396.03 |
| Appropriate comparator therapy | |
| Metformin | € 33.36 – 100.07 |
| Sulphonylurea<br>Glibenclamide or<br>Glimepiride | <br>€ 13.09 – 78.54<br>€ 29.79 – 152.41 |
| Empagliflozin | € 659.15 |

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

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Liraglutide | € 1,308.99 – 1,963.48 |
| Metformin + glibenclamide *or* metformin + glimepiride<br>Metformin + empagliflozin<br>Metformin + liraglutide<br>liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents | Total:<br>€ 46.45 – 178.61<br>€ 63.15 – 252.48<br>€ 692.51 – 759.22<br>€ 1,342.34 – 2,063.55 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

**Costs for additionally required SHI services:**

| Appropriate comparator therapy | | |
|---|---|---|
| Liraglutide | 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

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Medicinal product to be evaluated (dulaglutide in combination with at least two hypoglycaemic agents[7] (except insulin)) | |
| Dulaglutide | € 1,243.63 |
| Metformin | € 33.36 – 100.07 |
| Glibenclamide *or*<br>Glimepiride | € 13.09 – 78.54<br>€ 29.79 – 152.41 |
| dulaglutide + metformin + glibenclamide *or*<br>dulaglutide + metformin + glimepiride | Total:<br>€ 1,290.07 – 1,422.23<br>€ 1,306.77 – 1,496.11 |
| Appropriate comparator therapy | |
| Metformin | € 33.36 – 100.07 |

[7] 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 | Annual treatment costs per patient |
|---|---|
| Empagliflozin | € 659.15 |
| Liraglutide | € 1,308.99 – 1,963.48 |
| Human insulin (NPH insulin) | € 382.74 – 765.49 |
| Human insulin (NPH-insulin) + metformin | Total:<br>€ 416.10 – 865.56 |
| Human insulin (NPH insulin) + empagliflozin | € 1,041.90 – 1,424.64 |
| Human insulin (NPH insulin) + liraglutide<br>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 drugs, anticoagulants, and/or lipid-lowering agents | € 1,691.73 – 2,728.97 |
| Possibly therapy only with human insulin if, in accordance with the product information, metformin and empagliflozin and liraglutide are incompatible or contraindicated or are not sufficiently effective because of an advanced type 2 diabetes mellitus | |
| Conventional insulin therapy (mixed insulin) | € 382.70 – 765.39 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

**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 (mixed insulin) | Blood glucose test strips<br>Lancets<br>Disposable needles | € 116.44 – 349.31<br>€ 7.48 – 22.45<br>€ 61.69 – 123.37 |
| Liraglutide | Disposable needles | € 61.69 |
| Appropriate comparator therapy | | |
| Liraglutide | Disposable needles | € 61.69 |

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 renal insufficiency

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Medicinal product to be assessed (dulaglutide in combination with insulin (with or without another hypoglycaemic agent[8])) | |
| Dulaglutide | € 1,243.63 |
| Human insulin (NPH insulin) | € 382.74 – 765.49 |
| Possibly metformin | € 33.36 – 100.07 |
| dulaglutide + human insulin (NPH insulin) *or* dulaglutide + human insulin (NPH insulin) + metformin | Total:<br>€ 1,626.37 – 2,009.11<br><br>€ 1,659.73 – 2,109.18 |
| Appropriate comparator therapy | |
| Metformin | € 33.36 – 100.07 |
| Empagliflozin | € 659.15 |
| Liraglutide | € 1,308.99 – 1,963.48 |
| <u>Conventional insulin therapy (mixed insulin)</u><br><br><u>Conventional insulin therapy (mixed insulin) possibly + metformin *or* empagliflozin *or* liraglutide</u><br>Conventional insulin therapy (mixed insulin) + metformin<br>Conventional insulin therapy (mixed insulin) + empagliflozin<br>Conventional insulin therapy (mixed insulin) + liraglutide<br>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 drugs, anticoagulants, and/or lipid-lowering agents | € 382.74 – 765.49<br><br>Total:<br>€ 416.10 – 865.56<br><br>€ 1.041.90 – 1,424.64<br><br>€ 1,691.73 – 2,728.97 |
| <u>Intensified conventional insulin therapy</u><br>Human insulin (NPH insulin)<br>Human insulin (bolus insulin)<br>Total: | <br>€ 153.10 – 459.29<br>€ 153.10 – 459.29<br>Total:<br>€ 382.74 – 765.49 |

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

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

**Costs for additionally required SHI services:**

| Designation of the therapy | Designation | Costs/year |
|---|---|---|
| Medicinal product to be assessed (dulaglutide in combination with insulin (with or without another hypoglycaemic agent)) | | |
| Human insulin (NPH insulin) | Blood glucose test strips<br>Lancets<br>Disposable needles | € 116.44 – 349.31<br>€ 7.48 – 22.45<br>€ 61.69 – 123.37 |
| Appropriate comparator therapy | | |
| Conventional insulin therapy (mixed insulin) | Blood glucose test strips<br>Lancets<br>Disposable needles | € 116.44 – 349.31<br>€ 7.48 – 22.45<br>€ 61.69 – 123.37 |
| Intensified conventional insulin therapy | Blood glucose test strips<br>Lancets<br>Disposable needles | € 465.74 – 698.61<br>€ 29.93 – 44.90<br>€ 246.74 – 308.43 |
| Liraglutide | Disposable needles | € 61.69 |

d2) in patients with moderate or severe renal insufficiency in accordance with chronic kidney disease CKD stage 3 and 4 defined by an eGFR value < 60 to ≥ 15 ml/min/1.73 $m^2$

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Medicinal product to be assessed (dulaglutide in combination with insulin (with or without another hypoglycaemic agent[9])) | |
| Dulaglutide | € 1,243.63 |
| Human insulin (NPH insulin) | € 382.74 – 765.49 |
| Possibly metformin | € 33.36 – 100.07 |
| dulaglutide + human insulin (NPH insulin) *or* dulaglutide + human insulin (NPH insulin) + metformin | Total:<br>€ 1,626.37 – 2,009.11<br>€ 1,659.73 – 2,109.18 |
| Appropriate comparator therapy | |
| Metformin | € 33.36 – 100.07 |

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

| Designation of the therapy | Annual treatment costs per patient |
|---|---|
| Liraglutide | € 1,308.99 – 1,963.48 |
| <u>Conventional insulin therapy (mixed insulin)</u><br><br><u>Conventional insulin therapy (mixed insulin) possibly + metformin *or* liraglutide</u><br>Conventional insulin therapy (mixed insulin) + metformin<br><br>Conventional insulin therapy (mixed insulin) + liraglutide<br>liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents | € 382.74 – 765.49<br><br>Total:<br>€ 416.10 – 865.56<br><br>€ 1,691.73 – 2,728.97 |
| <u>Intensified conventional insulin therapy</u><br>Human insulin (NPH insulin)<br>Human insulin (bolus insulin)<br>Total: | <br>€ 153.10 – 459.29<br>€ 153.10 – 459.29<br>Total:<br>€ 382.74 – 765.49 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

**Costs for additionally required SHI services:**

| Designation of the therapy | Designation | Costs/year |
|---|---|---|
| Medicinal product to be assessed (dulaglutide in combination with insulin (with or without another hypoglycaemic agent)) | | |
| Human insulin (NPH insulin) | Blood glucose test strips<br>Lancets<br>Disposable needles | € 116.44 – 349.31<br>€ 7.48 – 22.45<br>€ 61.69 – 123.37 |
| Appropriate comparator therapy | | |
| Conventional insulin therapy (mixed insulin) | Blood glucose test strips<br>Lancets<br>Disposable needles | € 116.44 – 349.31<br>€ 7.48 – 22.45<br>€ 61.69 – 123.37 |
| Intensified conventional insulin therapy | Blood glucose test strips | € 465.74 – 698.61<br>€ 29.93 – 44.90 |

| Designation of the therapy | Designation | Costs/year |
|---|---|---|
| | Lancets<br>Disposable needles | € 246.74 – 308.43 |
| Liraglutide | Disposable needles | € 61.69 |

**II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 16 July 2020.**

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

Berlin, 16 July 2020

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

Prof. Hecken