Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Appendix XII – Resolutions on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V – Insulin degludec (Reassessment based on new scientific knowledge)

From 16. May 2019

At its meeting on16. May 2019, the Federal Joint Committee (G-BA) decided to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive) in the version dated 18 December 2008/22 January 2009 (BAnz. No. 49a of 31 March 2009), as last amended on TT. Monat JJJJ (BAnz AT TT.MM.JJJJ BX), as follows:

I. In Appendix XII the information on the active ingredient "Insulin degludec" in the version of the resolution of 16 October 2014 (BAnz AT 11.11.2014 B1) is amended as follows:

1. The information under "insulin degludec" is amended as follows:

   a. The information "16 October 2014" under "Resolution from:" is replaced by the following information: "16 October 2014 / 16 May 2019".

   b. The information "16 October 2014" under "entered into force on:" is replaced by the following information: "16 October 2014 / 16 May 2019".

2. The information under "Approved therapeutic indication" is amended as follows:

   "Therapeutic indication (according to the product information of November 2018):

   Treatment of diabetes mellitus in adults, young persons, and children aged 1 year and older.

   The following information relates exclusively to the therapeutic indication for the treatment of adult patients with diabetes mellitus."

3. Number 1. is amended as follows:

   a. The information on a), b), and c) is replaced by the following information:

   "<u>In the mono- or combination therapy</u>

   a) 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[1] *or*
   - Human insulin + liraglutide[1] *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 Insulin degludec compared to the appropriate comparator therapy:

   An additional benefit is not proven.

   b) 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

   Appropriate comparator therapy

   - The optimisation of the human insulin regimen (possibly + metformin *or* empagliflozin[1] *or* liraglutide[1])

   Extent and probability of the additional benefit of Insulin degludec compared to the appropriate comparator therapy:

   An additional benefit is not proven.

[1] 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-reducers (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).

b. Letter d) is replaced by letter c).

c. The following information is added at the end after the information referred to in point (c)

"Study results according to endpoints [2] of the DEVOTE study for patient groups a) and b) in adult patients with insufficiently controlled type 2 diabetes mellitus and manifest cardiovascular disease:

Endpoint category Endpoint	Intervention Insulin degludec		Control Insulin glargin		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	HR[a] [95% CI]; p value
Mortality					
Overall mortality	3818	202 (5.3)	3819	221 (5.8)	0.91 [0.76; 1.11]; 0.352
Morbidity					
Cardiovascular events (MACE)	3818	325 (8.5)	3819	356 (9.3)	0.91 [0.78; 1.06]; 0.209
Cardiovascular death[b]	3818	136 (3.6)	3819	142 (3.7)	0.96 [0.76; 1.21]; 0.714
Non-fatal stroke	3818	71 (1.9)	3819	79 (2.1)	0.90 [0.65; 1.23]; 0.502
Non-fatal myocardial infarction	3818	144 (3.8)	3819	169 (4.4)	0.85 [0.68; 1.06]; 0.150
Hospitalisation because of cardiac insufficiency	3818	296 (7.8)	3819	322 (8.4)	0.91 [0.78; 1.07]; 0.251
Health-related quality of life					
	Endpoint not recorded				
Side effects					
AEs (additionally shown)	*3818*	*1832 (48.0)*	*3819*	*1845 (48.3)*	-
SAEs	3818	1473 (38.6)	3819	1517 (39.7)	RR: 0.97 [0.92; 1.03]; 0.313
Withdrawal because of AEs	3818	200 (5.2)	3819	222 (5.8)	RR: 0.90 [0.75; 1.09]; 0.293
Non-severe, symptomatic, confirmed hypoglycaemias	Endpoint not recorded				
Severe hypoglycaemias in total (SAE)	3818	84 (2.2)	3819	78 (2.0)	RR: 1.08 [0.79; 1.46]; 0.635
Severe hypoglycaemias in total (SAE; in combination with glucose /glucagon; severe neuroglycopenic symptoms)	3818	157 (4.1)	3819	210 (5.5)	RR: 0.75 [0.61; 0.92]; 0.005
Renal dysfunction (SAE, SOC)	3818	144 (3.8)	3819	172 (4.5)	RR: 0.84 [0.67; 1.04]; 0.129[c]

a: unless identified otherwise
b: also takes into account 75 deaths with unknown cause
c: Calculation by the IQWiG, exact unconditional test (CSZ method according to Andrés)

Abbreviations:

[2] Data from the dossier assessment by the Institute for Quality and Efficiency in Health Care (IQWiG) (A18-84) of 27 February 2019 unless indicated otherwise.

CI: Confidence interval; MACE: Major adverse cardiovascular events; n: Number of patients with (at least one) event; N: Number of patients evaluated; RCT: Randomised Controlled Study; RR: Relative Risk; SOC: System Organ Class; SAE: Serious Adverse Event; AE: Adverse Event; vs: versus

Additionally presented endpoints of the DEVOTE study

	Intervention Insulin degludec			Control Insulin glargin			Intervention vs control
	N[a]	Values at the start of study MV (SD)	Change at the end of study MV[b] (SD)	N[a]	Values at the start of study MV (SD)	Change at the end of study MV[b] (SD)	MD [95% CI]; p value
HbA1c (%)	3818	8.35 (1.59)	−0.86 (0.02)	3819	8.31 (1.62)	−0.87 (0.02)	0.01[c] [−0.05; 0.07]; 0.779[c]
Body weight	3818	96.1 (22.9)	2.2 (7.3)	3819	96.1 22.9)	1.9 (7.3)	

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 the study can be based on other patient figures.
b: unless indicated otherwise, MMRM evaluation of the ITT population
c: MMRM with interactions between medical rounds and treatment and between medical rounds and baseline value as fixed effects

Abbreviations:
HbA1c: Glycohaemoglobin; ITT: Intention to Treat; CI: Confidence Interval; MD: Mean Value Difference; MMRM: mixed model with repeated measurements; MV: Mean Value; N: Number of evaluated patients; RCT: Randomised Controlled Study; SD: Standard Deviation; vs: versus

a) 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

Study results according to endpoints of the studies NN1250-3579 (52 weeks) with the extension study 3579Ext (further 52 weeks) as well as NN1250-3587 and NN1250 3672 (for each 26 weeks), dichotomous[2]

Endpoint category Endpoint Study	Intervention Insulin degludec +metformin		Control Insulin glargin +metformin		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Mortality					
Overall mortality					
NN1250-3579 (52 W)	519	0 (0)	151	1 (0.7)	n. c.; 0.225
NN1250-3587 (26 W)	366	0 (0)	191	1 (0.5)	n. c.; 0.343
NN1250-3672 (26 W)	139	0 (0)	139	1 (0.7)	n.c.; > 0.999
Total					0.18 [0.03; 1.13]; 0.067
3579Ext[a] (104 W)	519	2 (0.4)	151	1 (0.7)	0.58 [0.05; 6.37]; 0.536
Morbidity					
Cardiovascular events (MACE)					
NN1250-3579 (52 W)	518	9 (1.7)	151	1 (0.7)	2.62 [0.34; 20.54];

					0.470
NN1250-3587 (26 W)	364	0 (0)	191	2 (1.0)	0.11 [0.01; 2.18]; 0.052[b]
NN1250-3672 (26 W)	139	3 (2.2)	139	2 (1.4)	1.50 [0.25; 8.84]; > 0.999
Total					1.18 [0.35; 4.04]; 0.788
3579Ext[a] (104 W)	518	24 (4.6)	151	3 (2.0)	2.33 [0.71; 7.64]; 0.166
Cardiovascular death					
NN1250-3579 (52 W)	518	1 (0.2)	151	0 (0)	0.88 [0.04; 21.46][c]; 0.734[b]
NN1250-3587 (26 W)	364	0 (0)	191	0 (0)	n. c.
NN1250-3672 (26 W)	139	0 (0)	139	1 (0.7)	0.33 [0.01; 8.11][c]; 0.409[b]
Total					0.52 [0.06; 4.69]; 0.559[d]
3579Ext[a] (104 W)	518	2 (0.4)	151	1 (0.7)	0.58 [0.05; 6.39]; 0.536
Non-fatal stroke					
NN1250-3579 (52 W)	518	1 (0.2)	151	1 (0.7)	0.29 [0.02; 4.63]; 0.401
NN1250-3587 (26 W)	364	0 (0)	191	2 (1.0)	0.11 [0.01; 2.18];[c]; 0.052[b]
NN1250-3672 (26 W)	139	0 (0)	139	1 (0.7)	0.33 [0.01; 8.11[c]; 0.409[b]
Total					0.20 [0.04; 1.11]; 0.066[d]
3579Ext[a] (104 W)	518	6 (1.2)	151	2 (1.3)	0.87 [0.18; 4.29]; > 0.999
Acute coronary syndrome					
NN1250-3579 (52 W)	518	7 (1.4)	151	0 (0)	4.39 [0.25; 76.48];[c]; 0.158[b]
NN1250-3587 (26 W)	364	0 (0)	191	0 (0)	n. c.
NN1250-3672 (26 W)	139	3 (2.2)	139	0 (0)	7.00 [0.36; 134.27];[c]; 0.087[b]
Total					5.42 [0.70; 41.85]; 0.105[d]
3579Ext[a] (104 W)	518	17 (3.3)	151	0 (0)	OR: 7.21 [1.54; ∞]; 0.012[e]
Side effects					
AEs (additionally shown)					
NN1250-3579 (52 W)	*519*	*392 (75.5)*	*151*	*110 (72.8)*	–
NN1250-3587 (26 W)	*366*	*204 (55.7)*	*191*	*113 (59.2)*	–
NN1250-3672 (26 W)	*139*	*86 (61.9)*	*139*	*95 (68.3)*	–
3579Ext[a] (104 W)	*519*	*421 (81.1)*	*151*	*121 (80.1)*	–
SAEs					
NN1250-3579 (52 W)	519	40 (7.7)	151	18 (11.9)	0.65 [0.38; 1.09]; 0.137
NN1250-3587 (26 W)	366	10 (2.7)	191	9 (4.7)	0.58 [0.24; 1.40]; 0.228
NN1250-3672 (26 W)	139	10 (7.2)	139	8 (5.8)	1.25 [0.51; 3.07]; 0.808
Total					0.72 [0.48; 1.08]; 0.114
3579Ext[a] (104 W)	519	80 (15.4)	151	25 (16.6)	0.93 [0.62; 1.40]; 0.705
Withdrawal because of AEs					
NN1250-3579 (52 W)	519	14 (2.7)	151	2 (1.3)	2.04 [0.47; 8.86]; 0.544
NN1250-3587 (26 W)	366	2 (0.5)	191	2 (1.0)	0.52 [0.07; 3.68]; 0.610

NN1250-3672 (26 W)	139	2 (1.4)	139	2 (1.4)	1.00 [0.14; 7.00]; > 0.999
Total					1.17 [0.43; 3.21]; 0.755
3579Ext[a] (104 W)	519	21 (4.0)	151	4 (2.6)	1.53 [0.53; 4.38]; 0.625
Non-severe symptomatic, confirmed hypoglycaemias in total (PG < 56 mg/dl)					
NN1250-3579 (52 W)	519	175 (33.7)	151	57 (37.7)	0.89 [0.70; 1.13]; 0.382
NN1250-3587 (26 W)	366	97 (26.5)	191	55 (28.8)	0.92 [0.70; 1.22]; 0.617
NN1250-3672 (26 W)	139	23 (16.5)	139	29 (20.9)	0.79 [0.48; 1.30]; 0.442
Total					0.89 [0.75; 1.06]; 0.182
3579Ext[a] (104 W)	519	237 (45.7)	151	71 (47.0)	0.97 [0.80; 1.18]; 0.781
Severe hypoglycaemias (SAE)					
NN1250-3579 (52 W)	519	1 (0.2)	151	1 (0.7)	0.29 [0.02; 4.62]; 0.400
NN1250-3587 (26 W)	366	2 (0.5)	191	2 (1.0)	0.52 [0.07; 3.68]; 0.610
NN1250-3672 (26 W)	139	0 (0)	139	0 (0)	n. c.
Total					0.43 [0.09; 2.12]; 0.299
3579Ext[a] (104 W)	519	3 (0.6)	151	1 (0.7)	0.87 [0.09; 8.33]; > 0.999
Renal dysfunction (SAE, SOC)					
NN1250-3579 (52 W)	518	1 (0.2)	151	1 (0.7)	0.29 [0.02; 4.63][c];0.474[b]
NN1250-3587 (26 W)	364	0 (0)	191	0 (0)	n. c.
NN1250-3672 (26 W)	139	0 (0)	139	1 (0.7)	0.33 [0.01; 8.11][c]; 0.409[b]
Total					0.24 [0.02; 2.60]; 0.238[f]
3579Ext[a] (104 W)	518	3 (0.6)	151	3 (2.0)	0.29 [0.06; 1.43];[c]; 0.108[b]
Vomiting (AE, PT)					
NN1250-3579 (52 W)	518	15 (2.9)	151	9 (6.0)	0.49 [0.22; 1.09];[c]; 0.108[b]
NN1250-3587 (26 W)	364	3 (0.8)	191	2 (1.0)	0.79 [0.13; 4.67];[c]; 0.851[b]
NN1250-3672 (26 W)	139	4 (2.9)	139	3 (2.2)	1.33 [0.30; 5.85];[c]; 0.793[b]
Total					0.66 [0.34; 1.25]; 0.201[d]
3579Ext[a] (104 W)	518	18 (3.5)	151	12 (7.9)	0.44 [0.22; 0.89];[c]; 0.023[b]
Depression (AE, PT)					
NN1250-3579 (52 W)	518	6 (1.2)	151	0 (0)	3.81 [0.22; 67.20];[c]; 0.189[b]
NN1250-3587 (26 W)	364	2 (0.5)	191	0 (0)	2.63 [0.13; 54.51];[c]; 0.407[b]
NN1250-3672 (26 W)	139	0 (0)	139	1 (0.7)	0.33 [0.01; 8.11];[c]; 0.409[b]
Total					1.76 [0.37; 8.39]; 0.475[d]
3579Ext[a] (104 W)	518	15 (2.9)	151	0 (0)	OR: 6.30 [1.35; ∞]; 0.020[e]

a: Extension study to the NN1250-3579 study
b: Calculation by the IQWiG; p value from the exact unconditional test (CSZ method according to Andrés)
c: Calculation by the IQWiG; if there are zero cells with correction for continuity 0.5 for all cells
d: Calculation by the IQWiG, meta-analysis with fixed effect, Mantel-Haenszel method
e: Calculation by the IQWiG, exact conditional logistic regression according to Hirji; unilateral p value
f: Calculation by the IQWiG, meta-analysis with fixed effect, Beta binomial model according to Kuss

Abbreviations:
n.s.: not specified; CI: Confidence Interval; MACE: Major Adverse Cardiovascular Events; n: Number of patients with (at least 1) event; n.c.: not calculated; N: Number of patients evaluated; OR: Odds Ratio; PG: Plasma Glucose; PT: Preferred Term; RCT: Randomised Controlled Study; RR: Relative Risk; SOC: System Organ Class; SAE: Serious Adverse Event; AE: Adverse Event; vs: versus; W: Weeks

Study results according to endpoints of the studies NN1250-3579 (52 weeks) with the extension study 3579Ext (further 52 weeks) as well as NN1250-3587 and NN1250 3672 (for each 26 weeks), continuous[2]

Endpoint category Endpoint Study	Intervention Insulin degludec + metformin			Control Insulin glargin + metformin			Intervention vs control
	N[a]	Values at the start of study MV (SD)	Change at the end of study MV[b] (SE)	N[a]	Values at the start of study MV (SD)	Change at the end of study MV[b] (SE)	MD [95% CI]; p value
Morbidity							
State of health							
TRIM-D[c]							
Daily life							
NN1250-3579 (52 W)	519	77.79 (18.9)	3.57 (0.80)	151	76.14 (20.1)	2.70 (1.51)	0.87 [−2.49; 4.23]; 0.611
NN1250-3587 (26 W)	366	75.22 (17.8)	3.17 (0.84)	191	76.65 (16.1)	2.85 (1.19)	0.33 [−2.55; 3.20]; 0.824
NN1250-3672 (26 W)	139	76.08 (19.6)	3.50 (1.31)	139	77.78 (19.3)	3.81 (1.31)	−0.31 [−3.98; 3.35]; 0.867
Total							0.33 [−1.55; 2.21]; 0.730
3579Ext[a] (104 W)	Endpoint not recorded						
Mental health							
NN1250-3579 (52 W)	519	77.51 (17.3)	8.69 (0.69)	151	75.66 (18.5)	8.86 (1.30)	−0.17 [−3.06; 2.72]; 0.906
NN1250-3587 (26 W)	366	73.21 (19.2)	7.45 (0.79)	191	73.7 (18.6)	6.26 (1.12)	1.19 [−1.51; 3.89]; 0.388
NN1250-3672 (26 W)	139	76.01 (17.6)	8.87 (1.24)	139	77.95 (17.3)	5.76 (1.24)	3.11 [−0.36; 6.59]; 0.079
Total							1.18 [−0.54; 2.89]; 0.178
3579Ext[a] (104 W)	Endpoint not recorded						
HbA1c [%] additionally shown)							

NN1250-3579 (52 W)	*519*	*8.18 (0.8)*	*−1.16 (0.03)*	*151*	*8,31. (0.8)*	*−1.33 (0.06)*	*0.17 [0.03; 0.31]; 0.019*
NN1250-3587 (26 W)	*366*	*8.32.(0.83)*	*−1.25 (0.04)*	*191*	*8.28 (0.81)*	*−1.24 (0.06)*	*−0.01 [−0.16; 0.14]; 0.901*
NN1250-3672 (26 W)	*139*	*8.35 (0.99)*	*−1.25 (0.08)*	*139*	*8.33 (0.82)*	*−1.27 (0.08)*	*0.02 [−0.19; 0.23]; 0.877*
Total							*0.07 [−0.02; 0.17]; 0.117*
3579Ext[a] (104 W)	*519*	*8.14 (0.78)*	*−1.13 (0.04)*	*151*	*8.27 (0.79)*	*−1.26 (0.07)*	*0.12 [−0.03; 0.28]; 0.127*
Health-related quality of life							
SF-36[e]							
Physical component score (PCS)							
NN1250-3579 (52 W)	*519*	*46.3 (8.7)*	*1.10 (0.32)*	*151*	*44.9 (9.22)*	*−0.78 (0.60)*	1.88 [0.56; 3.21]; 0.006 Hedges' g: *0.31 [0.11; 0.52]*
NN1250-3587 (26 W)	*366*	*48.13 (7.62)*	*1.01 (0.33)*	*191*	*47.69 (7.39)*	*0.63 (0.46)*	0.38 [−0.74; 1.50]; 0.503
NN1250-3672 (26 W)	*139*	*44.62 (9.23)*	*1.84 (0.58)*	*139*	*45.91 (8.24)*	*1.42 (0.59)*	0.42 [−1.21; 2.06]; 0.611
Total							0.88 [0.12; 1.64]; 0.023
					Heterogeneity for Hedges' g:		Q = 6.45, df = 2, p = 0.040, I^2 = 69.0%
3579Ext[a] (104 W)	*519*	*46.78 (8.73)*	*−0.14 (0.38)*	*151*	*46.28 (9.13)*	*−2.02 (0.74)*	1.88 [0.25; 3.52]; 0.024 Hedges' g: 0.26 [0.00; 0.51]
Mental Component Score (MCS)							
NN1250-3579 (52 W)	*519*	*48.76 (11.3)*	*1.05 (0.41)*	*151*	*48.33 (11.4)*	*1.46 (0.77)*	−0.40 [−2.12; 1.32]; 0.645
NN1250-3587 (26 W)	*366*	*47.38 (10.7)*	*0.92 (0.44)*	*191*	*47.82 (10.0)*	*0.74 (0.62)*	0.19 [−1.31; 1.68]; 0.806
NN1250-3672 (26 W)	*139*	*47.52 (11.7)*	*2.37 (0.77)*	*139*	*47.49 (10.7)*	*0.67 (0.78)*	1.71 [−0.47; 3.88]; 0.125
Total							0.31 [−0.69; 1.31]; 0.541
3579Ext[a] (104 W)	*519*	*50.06 (10.9)*	*0.70 (0.48)*	*151*	*50.26 (9.92)*	*0.05 (0.95)*	0.65 [−1.43; 2.73]; 0.541
individual domains of the SF-36	No findings for the relevant subpopulation available						

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 the study can be based on other patient figures.
b: unless indicated otherwise, MMRM evaluations of the FAS population with treatment, gender, anti-diabetic therapy on baseline, and region as fixed effect; corresponding baseline value and age as covariant as well as the interaction between all fixed effects and medical rounds and between the baseline value and medical rounds
c: higher values mean an improvement of the state of health, whereby a positive difference signifies an advantage of the intervention; data on the individual domains are not available for the sub-populations
d: Extension study to the NN1250-3579 study
e: higher values signify a better health-related quality of life; a positive difference signifies an advantage for the intervention

Abbreviations:
FAS: Full Analysis Set; HbA1c: Glycohaemoglobin; CI: Confidence Interval; MMRM: Mixed Model with Repeated Measurements; MD: Mean Value Difference; MV: Mean Value; N: Number of evaluated patients; RCT: Randomised Controlled Study; SD: Standard Deviation; SE: Standard Error; SF-36: Short Form-36 Health Survey; TRIM-D: Treatment-related Impact Measures for Diabetes; vs: versus; W: Weeks

On b) 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

Study results according to endpoints of the NN1250-3582 study (52 weeks) and the extension study to the NN1250-3582 study (78 weeks), dichotomous[2]

Study **Endpoint category** **Endpoint** **Date**	**Intervention** **Insulin degludec + metformin + insulin aspart**		**Control** **Insulin glargin + metformin + insulin aspart**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Mortality					
Overall mortality					
52 weeks	744	8 (1.1)	248	2 (0.8)	1.33 [0.29; 6.24]; > 0.999
78 weeks	744	11 (1.5)	248	2 (0.8)	1.83 [0.41; 8.21]; 0.536
Morbidity					
Cardiovascular events (MACE)					
52 weeks	742	18 (2.4)	248	4 (1.6)	1.50 [0.51; 4.40]; 0.620
78 weeks	742	29 (3.9)	248	7 (2.8)	1.38 [0.61; 3.12]; 0.557
Cardiovascular death					
52 weeks	742	4 (0.5)	248	1 (0.4)	1.34 [0.15; 11.91]; > 0.999
78 weeks	742	5 (0.7)	248	1 (0.4)	1.67 [0.20; 14.24]; > 0.999
Non-fatal stroke					
52 weeks	742	3 (0.4)	248	0 (0)	n.s.; 0.577
78 weeks	742	7 (0.9)	248	0 (0)	n.s.; 0.202
Acute coronary syndrome					
52 weeks	742	11 (1.5)	248	3 (1.2)	1.23 [0.34; 4.36]; > 0.999
78 weeks	742	17 (2.3)	248	6 (2.4)	0.95 [0.38; 2.38]; > 0.999
Side effects					
AEs (additionally shown)					

52 weeks	*744*	*605 (81.3)*	*248*	*199 (80.2)*	-
78 weeks	*744*	*625 (84.0)*	*248*	*208 (83.9)*	-
SAEs					
52 weeks	744	111 (14.9)	248	40 (16.1)	0.93 [0.66; 1.29]; 0.683
78 weeks	744	138 (18.5)	248	53 (21.4)	0.87 [0.65; 1.15]; 0.353
Withdrawal because of AEs					
52 weeks	744	31 (4.2)	248	9 (3.6)	1.15 [0.55; 2.38]; 0.853
78 weeks	744	35 (4.7)	248	9 (3.6)	1.30 [0.63; 2.66]; 0.594
Non-severe symptomatic, confirmed hypoglycaemias in total (PG < 56 mg/dl)					
52 weeks	744	556 (74.7)	248	188 (75.8)	0.99 [0.91; 1.07]; 0.800
78 weeks	744	581 (78.1)	248	192 (77.4)	1.01 [0.93; 1.09]; 0.860
Severe hypoglycaemias (SAE)					
52 weeks	744	19 (2.6)	248	3 (1.2)	2.11 [0.63; 7.07]; 0.319
78 weeks	744	20 (2.7)	248	3 (1.2)	2.22 [0.67; 7.41]; 0.228
Renal dysfunction (SAE, SOC)					
52 weeks	753	2 (0.3)	251	2 (0.8)	0.33 [0.05; 2.35]; 0.257[b]
78 weeks	753	2 (0.3)	251	3 (1.2)	0.22 [0.04; 1.32]; 0.071[b]

a: Extension study to the NN1250-3582 study

b: Calculation by the IQWiG; p value from the exact unconditional test (CSZ method according to Andrés)

Abbreviations:

n.s.: not specified; CI: Confidence Interval; MACE: Major adverse cardiovascular events; n: Number of patients with (at least one) event; N: Number of patients evaluated; n.c.: not calculated; PG: Plasma Glucose; RCT: Randomised Controlled Study; RR: Relative Risk; SOC: System Organ Class; SAE: Serious Adverse Event; AE: Adverse Event; vs: versus

Study results according to endpoints of the NN1250-3582 study (52 weeks) and the extension study to the NN1250-3582 study (78 weeks), continuous[2]

Study **Endpoint category** **Endpoint** **Date**	**Intervention** **Insulin degludec + metformin + insulin aspart**			**Control** **Insulin glargin + metformin + insulin aspart**			**Intervention vs control**
	N[a]	Values at the start of study MV (SD)	Change at the end of study MV (SE)	N[a]	Values at the start of study MV (SD)	Change at the end of study MV (SE)	MD [95% CI]; p value
Morbidity							
State of health							
TRIM-D[b]							
Daily life							
52 weeks	744	72.05 (18.2)	3.02 (0.67)	248	72.43 (17.5)	2.88 (1.15)	0.14 [−2.48; 2.75]; 0.919
78 weeks	Endpoint not recorded						
Mental health							
52 weeks	744	75.87 (17.3)	5.14 (0.61)	248	73.67 (18.7)	5.26 (1.06)	−0.12 [−2.52; 2.29]; 0.924

78 weeks	Endpoint not recorded						
Health-related quality of life							
SF-36v2[b]							
PCS							
52 weeks	744	45.25 (9.25)	−0.35 (0.28)	248	44.53 (8.89)	−0.64 (0.48)	0.28 [−0.80; 1.37]; 0.609
78 weeks	Endpoint not recorded						
MCS							
52 weeks	744	47.89 (11.2)	1.21 (0.34)	248	48.72 (10.6)	0.29 (0.59)	0.92 [−0.42; 2.26]; 0.176
78 weeks	Endpoint not recorded						

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 the study can be based on other patient figures.
b: higher values signify a better health-related quality of life; a positive difference signifies an advantage for the intervention

Abbreviations:
n.s.: not specified; CI: Confidence Interval; MCS: Mental Component Score; MD: Mean Value Difference; MV: Mean Value; N: Number of patients evaluated; PCS: Physical Component Score; RCT: Randomised Controlled Study; SD: Standard Deviation; SE: Standard Error; TRIM-D: Treatment-related Impact Measures for Diabetes; vs: versus

Study results according to endpoints of the NN1250-3582 study (52 weeks) and the extension study to the NN1250-3582 study (78 weeks)

Study Endpoint Date	**Intervention Insulin degludec + metformin + insulin aspart**			**Control Insulin glargin + metformin + insulin aspart**			**Intervention vs control**
	N[a]	Values at the start of study MV (SD)	Change at the end of study MV (SE)	N[a]	Values at the start of study MV (SD)	Change at the end of study MV (SE)	MD [95% CI]; p value
HbA1c (%)							
52 weeks	744	8.25 (0.79)	−1.28 (0.03)	248	8.34 (0.89)	−1.28 (0.05)	0.01 [−0.11; 0.12]; 0.906
78 weeks	744	8,24 (0.79)	−1.01 (0.03)	248	8.32 (0.89)	−1.14 (0.05)	0.13 [0.00; 0.25]; 0.048
Body weight							
52 weeks	622	92.6 (17.9)	3.9 (5.0)	211	92.2 (17.2)	4.2 (4.8)	−0.31 [−0.98; 0.37]; n.s.
78 weeks	544	92.6 (17.9)	4.4 (5.1)	184	92.2 (17.2)	4.7 (4.9)	−0.34 [−1.05; 0.38]; n.s.

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 the study can be based on other patient figures.

Abbreviations:
n.s.: not specified; CI: Confidence Interval; MD: Mean Value Difference; MV: Mean Value; N: Number of evaluated patients; RCT: Randomised Controlled Study; SD: Standard Deviation; SE: Standard error; vs: versus

"

4. Number 2. is amended as follows:

a. Under number 2, the entries for (a), (b), and (c) are replaced by the following:

"a) 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. 326,100–341,100 patients

b) 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. 450,000–650,000 patients"

b. Letter d) is replaced by letter c).

5. Under number 3, the information on the requirement for a quality-assured application is formulated as follows:

The requirements of the product information must be taken into account. The European Medicines Agency (EMA) makes the contents of the product information on Tresiba® (active ingredient: Insulin degludec) freely available under the following link (last access: 12. April 2019):
https://www.ema.europa.eu/documents/product-information/xultophy-epar-product-information_de.pdf

"

6. Number 4. is amended as follows:

a. The information on a), b) and c) is replaced by the following information:

"Annual treatment costs:

a) 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 assessed (insulin degludec alone or in combination with an oral hypoglycaemic agent[3])	
Insulin degludec	€ 452.72 – € 905.45
Metformin	€ 33.24 – € 99.71
Total:	
Insulin degludec + metformin	€ 485.96 – € 1005.16
Appropriate comparator therapy	
Metformin	€ 33.24 – € 99.71

[3] An example of the combination with a hypoglycaemic agent (apart from insulin) is the combination with metformin.

Designation of the therapy	Annual treatment costs per patient
Empagliflozin	€ 658.93
Liraglutide	€ 1,308.84 – € 1,963.26
Human insulin (NPH insulin)	€ 382.46 – € 764.92
Human insulin (NPH-insulin) + metformin	Total: € 415.70 – € 864.63
Human insulin (NPH insulin) + empagliflozin[1]	€ 1,041.40 – € 1,423.86
Human insulin (NPH insulin) + empagliflozin[1]	€ 1,691.30 – € 2,728.19
Possibly therapy only with human insulin if metformin and empagliflozin[1] and liraglutide[1] in accordance with the product information 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 legally prescribed rebates (Lauer-Taxe® last revised: 15. April 2019)

Costs for additional SHI services required: omitted

b) 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

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed (insulin degludec in combination with a hypoglycaemic agent[4] and bolus insulin)	
Insulin degludec	€ 452.72 – € 905.45
Insulin degludec Bolus insulin Total:	€ 181.09 – € 543.27 € 152.98 – € 458.95 € 410.57 – € 849.24
Possibly metformin	€ 33.24 – € 99.71
Total:	
Insulin degludec + metformin	€ 485.96 – € 1005.16

[4] For example, for the combination with a hypoglycaemic agent, metformin is stated

Designation of the therapy	Annual treatment costs per patient
Insulin degludec + bolus insulin	€ 410.57 – € 849.24
Insulin degludec + bolus insulin or	€ 443.80 – € 948.95
Appropriate comparator therapy	
Empagliflozin	€ 658.93
Liraglutide	€ 1,308.84 – € 1,963.26
Metformin	€ 33.24 – € 99.71
Intensified conventional insulin therapy Human insulin (NPH insulin) Human insulin (bolus insulin)	 € 152.98 – € 458.95 € 152.98 – € 458.95 Total: € 382.46 – € 764.92
Conventional insulin therapy (premixed insulin) Conventional insulin therapy (premixed insulin) possibly + metformin or empagliflozin or liraglutide Conventional insulin therapy (premixed insulin) + empagliflozin[1] Conventional insulin therapy (premixed insulin) + liraglutide[1] Conventional insulin therapy (premixed insulin) + metformin	€ 382.46 – € 764.92 Total: € 1,041.40 – € 1,423.86 € 1,691.30 – € 2,728.19 € 415.70 – € 864.63

Costs after deduction of legally prescribed rebates (Lauer-Taxe® last revised: 15. April 2019)

Costs for additional SHI services required: omitted".

b. In the heading "d) Treatment of type 1 diabetes mellitus in adults" letter "d)" is replaced by letter "c)".

c. The tables "Costs for additional SHI services required" and "Annual treatment costs" under the heading "c) Treatment of type 1 diabetes mellitus in adults" is supplemented by the following sentence:

Costs after deduction of legally prescribed rebates (Lauer-Taxe® last revised: 1 October 2014)".

d. The previous footnote 1 is now footnote 8.

e. The previous footnote 2 is now footnote 9.

f. The previous footnote 3 is now footnote 10.

g. The previous footnote 4 is now footnote 12.

h. The previous footnote 5 is now footnote 13.

i. The previous footnote 6 is now footnote 14.

j. The previous footnote 8 is now footnote 16.

k. The previous footnote 14 is now footnote 5.

l. The previous footnote 15 is now footnote 7.

m. The previous footnote 17 is now footnote 11.

n. The previous footnote 19 is now footnote 6.

o. The previous footnote 20 is now footnote 15.

p. The previous footnotes 7, 9, 10, 11, 12, 13, 16, and 18 are omitted.

7. The provision on the entry into force in II. is revoked.

II. The resolution will enter into force on the day of its publication on the Internet on the websites of the G-BA on 16. May 2019.

The justification for this resolution is published on the websites of the G-BA under www.g-ba.de.

Berlin, 16. May 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof Hecken