Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Insulin icodec (type 1 diabetes mellitus)

of 20 February 2025

At its session on 20 February 2025, the Federal Joint Committee (G-BA) resolved to amend the 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Insulin icodec in the version of the resolution of 20 February 2024 on the therapeutic indication "Treatment of type 2 diabetes mellitus in adults":

Insulin icodec

Resolution of: 20 February 2025
Entry into force on: 20 February 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 17 May 2024):

Treatment of diabetes mellitus in adults.

Therapeutic indication of the resolution (resolution of 20 February 2025):

Treatment of type 1 diabetes mellitus in adults.

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

Adults with type 1 diabetes mellitus

Appropriate comparator therapy

– Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin degludec, insulin aspart, insulin glulisine, insulin lispro)

Extent and probability of the additional benefit of insulin icodec in combination with insulin aspart compared with insulin degludec in combination with insulin aspart:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with type 1 diabetes mellitus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	∅	No data available.
Side effects	↓	Disadvantage in detail for the specific AE of serious 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 ∅: No data available. n.a.: not assessable		

ONWARDS 6 study: Insulin icodec + insulin aspart vs insulin degludec + insulin aspart

Mortality

Endpoint	Insulin icodec + insulin aspart		Insulin degludec + insulin aspart		Insulin icodec + insulin aspart vs Insulin degludec + insulin aspart
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Overall mortality[b]					
	290	1 (0.3)	292	0 (0)	3.02 [0.12; 73.84]; 0.370

[1] Data from the dossier assessment of the IQWiG (A24-90) and from the addendum (A25-02), unless otherwise indicated.

Morbidity

Endpoint	**Insulin icodec + insulin aspart**			**Insulin degludec + insulin aspart**			**Insulin icodec + insulin aspart vs Insulin degludec + insulin aspart**
	N	Patients with event n (%)		N	Patients with event n (%)		RR [95% CI] p value[a]
Acute coronary syndrome[c]	290	1 (0.3)		292	2 (0.7)		0.50 [0.05; 5.52]; 0.683
Cerebrovascular events[d]	290	2 (0.7)		292	1 (0.3)		2.01 [0.18; 22.09]; 0.602
Heart failure[e]	290	1 (0.3)		292	0 (0)		3.02 [0.12; 73.94]; 0.370
End-stage renal disease	No suitable data[f]						
Diabetic retinopathies	No suitable data[g]						
	N[h]	Values at the start of the study MV (SD)	Change at week 52 MV (SD)[b]	N[h]	Values at the start of the study MV (SD)	Change at week 52 MV (SD)[b]	MD [95% CI]; p-value[i]
HbA1c [%][j]	270	7.59 (0.96)	-0.37 (0.05)	278	7.63 (0.93)	-0.54 (0.05)	0.17 [0.02; 0.31]; 0.021
Body weight [kg] *(presented additionally)*	273	78.65 (17.62)	1.25 (0.27)	279	77.10 (16.78)	1.67 (0.29)	-0.42 [−1.20; 0.37]; 0.296

Health-related quality of life

The endpoint of health-related quality of life was not assessed in the ONWARDS 6 study.

Side effects

Endpoint	Insulin icodec + insulin aspart		Insulin degludec + insulin aspart		Insulin icodec + insulin aspart vs Insulin degludec + insulin aspart
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Total adverse events (presented additionally)					
	290	240 (82.8)	292	236 (80.8)	-
Serious adverse events (SAE)					
	290	24 (8.3)	292	21 (7.2)	1.15 [0.66; 2.02]; 0.683
Therapy discontinuation due to adverse events					
	290	2 (0.7)	292	1 (0.3)	2.01 [0.18; 22.09]; 0.602
Specific adverse events					
Non-severe symptomatic, confirmed hypoglycaemias					
PG < 54 mg/dl	No suitable data[m]				
PG < 70 mg/dl	No suitable data[m]				
Severe hypoglycaemias[k]	290	11 (3.8)	292	6 (2.1)	1.85 [0.69; 4.93]; 0.248
Serious hypoglycaemias (PT, SAE)	290	8 (2.8)	292	1 (0.3)	8.06 [1.01; 64.00]; 0.018
Diabetic ketoacidoses (PT, AE)	290	1 (0.3)	292	0 (0)	3.02 [0.12; 73.84][l]; 0.370

a. IQWiG calculation, unconditional exact test, CSZ method according to Andrés et al, 1994.
b. The results on overall mortality are based on the data on fatal AEs.
c. Includes the following adjudicated events: all types of acute myocardial infarction and unstable angina pectoris requiring hospitalisation
d. Includes strokes after adjudication of the following events: Stroke or transient ischaemic attack (episode of focal or global neurological dysfunction caused by brain, spinal cord or retinal vascular injury as a result of haemorrhage or ischaemia, with or without infarction)
e. Described by the pharmaceutical company in Module 4 C of the dossier as heart failure or myocardial infarction; the study documents indicate that the endpoint includes the following adjudicated events: new episode or deterioration of existing heart failure that led to urgent, unscheduled hospitalisation or a visit to a clinic/ practice/ emergency room
f. The study did not include a dedicated survey of end-stage renal disease.

g. The study did not include a dedicated survey of diabetic retinopathies.
h. Number of patients who were taken into account in the effect estimate; the values at the start of the study (and at week 52) can be based on other patient numbers.
i. ANCOVA model, adjusted for treatment, HbA1c value at screening < 8% (yes/ no), basal insulin treatment 2 × daily or with insulin glargine 300 U/ml prior to enrolment in the study (yes/ no) and geographical region as fixed factors and the baseline value as covariate; missing values replaced by multiple imputation
j. Sufficiently valid surrogate for microvascular secondary complications
k. Defined by the following criteria: required the assistance of healthcare professionals for treatment with glucagon or glucose IV; were life-threatening; resulted in hospitalisation or were characterised by severe neuroglycopenic symptoms
l. IQWiG calculation: RR [95% CI] (asymptotic)
m. According to the pharmaceutical company, collection of symptoms may not have been fully followed up, although this was intended according to the CRF, which is why no suitable data are available overall for non-severe symptomatic, confirmed hypoglycaemias.

Abbreviations used:
CRF: case report form; HbA1c: glycated haemoglobin; n.d.: no data available; CI: confidence interval; MD: mean difference; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; PG: plasma glucose; PT: preferred term; PC = pharmaceutical company; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; AE: adverse event; vs: versus.

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

Adults with type 1 diabetes mellitus

Approx. 161,750 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 Awiqli (active ingredient: insulin icodec) at the following publicly accessible link (last access: 27 January 2025):

https://www.ema.europa.eu/en/documents/product-information/awiqli-epar-product-information_en.pdf

In patients and patients with type 1 diabetes mellitus treated with insulin icodec, there was an increased risk of hypoglycaemia compared with insulin degludec (see sections 4.8 and 5.1 of the product information for Awiqli). Patients with type 1 diabetes mellitus should only be treated with insulin icodec if a clear benefit is expected from once-weekly dosage. The safety and efficacy of insulin icodec in newly diagnosed insulin-naive patients with type 1 diabetes mellitus have not been established. No data available.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for

medical professionals and patients. The training material[2] contains, in particular, information on the use of insulin icodec for once-weekly administration as well as warnings about the risk of confusion with other insulins.

4. Treatment costs

Annual treatment costs:

Adults with type 1 diabetes mellitus

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Insulin icodec	€ 330.90 - € 992.69
Concomitant active ingredient of the medicinal product to be assessed:	
Intensified insulin therapy (ICT) + insulin icodec Insulin icodec Human insulin (bolus insulin) Insulin icodec + human insulin (bolus insulin)	 € 330.90 - € 992.69 € 155.02 - € 465.06 Total: € 563.43 - € 1,302.73
Appropriate comparator therapy:	
Intensified insulin therapy (ICT) + human insulin Human insulin (NPH insulin) Human insulin (bolus insulin) Human insulin (NPH insulin) + human insulin (bolus insulin)	 € 155.02 - € 465.06 € 155.02 - € 465.06 Total: € 387.55 - € 775.10
Long-acting insulin analogues	
Intensified insulin therapy (ICT) + insulin degludec Insulin degludec Human insulin (bolus insulin) Insulin degludec + human insulin (bolus insulin)	 € 183.38 - € 550.14 € 155.02 - € 465.06 Total: € 415.91 - € 860.18
Intensified insulin therapy (ICT) + insulin detemir Insulin detemir Human insulin (bolus insulin) Insulin detemir + human insulin (bolus insulin)	 € 311.78 - € 935.33 € 155.02 - € 465.06 Total: € 544.31 - € 1,245.37
Intensified insulin therapy (ICT) + insulin glargine Insulin glargine Human insulin (bolus insulin)	 € 158.55 - € 475.66 € 155.02 - € 465.06

[2] Educational materials for healthcare professionals and patients using the diabetes medicine Awiqli: https://www.ema.europa.eu/en/documents/medication-error/awiqli-measures-intended-reduce-risk-confusion-dosing-requirements_en.pdf [accessed 11 February 2025].

Designation of the therapy	Annual treatment costs/ patient
Insulin glargine + human insulin (bolus insulin)	Total: € 391.08 - € 785.70
Short-acting insulin analogues	
<u>Intensified insulin therapy (ICT) + insulin aspart</u> Human insulin (NPH insulin) Insulin aspart Human insulin (NPH insulin) + insulin aspart	 € 155.02 - € 465.06 € 158.55 - € 475.66 Total: € 391.08 - € 785.70
<u>Intensified insulin therapy (ICT) + insulin gluisine</u> Human insulin (NPH insulin) Insulin glulisine Human insulin (NPH insulin) + insulin glulisine	 € 155.02 - € 465.06 € 219.91 - € 659.72 Total: € 452.44 - € 969.76
<u>Intensified insulin therapy (ICT) + insulin lispro</u> Human insulin (NPH insulin) Insulin lispro Human insulin (NPH insulin) + insulin lispro	 € 155.02 - € 465.06 € 189.60 - € 568.80 Total: € 422.13 - € 878.84

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2025)

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/ year
Medicinal product to be assessed:		
Insulin icodec	Blood glucose test strips Lancets	€ 18.70 - € 56.11 € 1.09 - € 3.28
Concomitant active ingredient of the medicinal product to be assessed:		
Human insulin (Bolus insulin)	Blood glucose test strips Lancets Disposable needles	€ 393.11 € 23.00 € 142.35
Appropriate comparator therapy:		
Human insulin (NPH insulin) + human insulin (bolus insulin)	Blood glucose test strips Lancets Disposable needles	€ 524.14 - € 786.21 € 30.66 - € 45.99 € 189.80 - € 237.25
Insulin degludec + human insulin (bolus insulin)	Blood glucose test strips Lancets Disposable needles	€ 524.14 - € 786.21 € 30.66 - € 45.99 € 189.80
Insulin detemir + human insulin (bolus insulin)	Blood glucose test strips Lancets Disposable needles	€ 524.14 - € 786.21 € 30.66 - € 45.99 € 189.80 - € 237.25

Designation of the therapy	Designation	Costs/ year
Insulin glargine + human insulin (bolus insulin)	Blood glucose test strips Lancets Disposable needles	€ 524.14 - € 786.21 € 30.66 - € 45.99 € 189.80
Human insulin (NPH insulin) + insulin aspart	Blood glucose test strips Lancets Disposable needles	€ 524.14 - € 786.21 € 30.66 - € 45.99 € 189.80 - € 237.25
Human insulin (NPH insulin) + insulin glulisine	Blood glucose test strips Lancets Disposable needles	€ 524.14 - € 786.21 € 30.66 - € 45.99 € 189.80 - € 237.25
Human insulin (NPH insulin) + insulin lispro	Blood glucose test strips Lancets Disposable needles	€ 524.14 - € 786.21 € 30.66 - € 45.99 € 189.80 - € 237.25

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with type 1 diabetes mellitus

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 February 2025.

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

Berlin, 20 February 2025

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

Prof. Hecken