Insulin icodec (type 1 diabetes mellitus)

Addendum to Project A24-90 (dossier assessment)[1]

ADDENDUM

Project: A25-02 Version: 1.0 Status: 30 Jan 2025 DOI: 10.60584/A25-02_en

[1] Translation of the addendum *Insulin icodec (Diabetes mellitus Typ 1) – Addendum zum Projekt A24-90 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Insulin icodec (type 1 diabetes mellitus) – Addendum to Project A24-90

Commissioning agency

Federal Joint Committee

Commission awarded on

7 January 2025

Internal Project No.

A25-02

https://doi.org/10.60584/A25-02_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50670 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Drug (Anwendungsgebiet); Benefit assessment according to §35a SGB V (new scientific findings, expiry of the decision); Extract [online]. dd XXX 20yy [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-02_en.

Keywords

Insulin Icodec, Diabetes Mellitus – Type 1, Benefit Assessment, NCT04848480

IQWiG employees involved in the addendum

- Christof Dücker
- Ulrich Grouven
- Kirsten Janke
- Daniela Preukschat

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CGM	continuous glucose monitoring
CRF	Case Report Form
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PG	plasma glucose
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 7 January 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-90 (Insulin icodec – Benefit assessment according to § 35a Social Code Book V) [1].

Following the oral hearing, the pharmaceutical company (hereinafter referred to as "the company") presented additional data that go beyond the information in the dossier. The commission comprised the assessment of the data presented by the company following the oral hearing [2], taking into account the information in the dossier [3]:

- Results for the outcome of non-severe, symptomatic hypoglycaemic episodes for the plasma glucose (PG) threshold value of 70 mg/dL

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The randomized controlled trial (RCT) ONWARDS 6 was used for the benefit assessment of insulin icodec in comparison with the appropriate comparator therapy (ACT) insulin degludec (both in combination with the bolus insulin insulin aspart). A detailed description of the study can be found in dossier assessment A24-90.

For the outcome of non-severe, symptomatic, confirmed hypoglycaemic episodes (PG < 70 mg/dL), no suitable data were available for the benefit assessment [1]. Following the oral hearing, the company subsequently submitted analyses on this outcome for the ONWARDS 6 study.

In accordance with the commission, the analyses subsequently submitted by the company are assessed below, taking into account the information in the dossier.

2.1 Data on non-severe symptomatic, confirmed hypoglycaemic episodes subsequently submitted by the company

The benefit assessment does not consider severe hypoglycaemic episodes, which are confirmed by falling below certain PG thresholds. In order for it to be assumed that these are patient-relevant events, the hypoglycaemic episodes must also be accompanied by symptoms.

According to the study design, hypoglycaemic episodes were recorded as soon as the results of the continuous glucose monitoring (CGM) fell below a PG value of 70 mg/dL in the ONWARDS 6 study, regardless of the presence of symptoms. If this value was also undercut in the subsequent self-measurement, the hypoglycaemic episode was recorded as an event in the electronic diary, carbohydrates were administered and the doses of the blood glucose-lowering therapy were adjusted. In addition, according to the study design, the analysis of clinically significant hypoglycaemic episodes with a PG value below 54 mg/dL was planned regardless of the occurrence of symptoms.

In the dossier, the company presented post hoc analyses of non-severe hypoglycaemic episodes associated with symptoms, but only for the PG threshold value of 54 mg/dL. As described in the dossier assessment, it would also have been possible for the company to conduct post hoc analyses on symptomatic events for the PG threshold of 70 mg/dL. However, such analyses were neither presented in the dossier nor subsequently submitted with the company's comments [4]. Moreover, it was discussed in the dossier assessment that in the ONWARDS 6 study, the proportion of patients with non-severe, confirmed symptomatic hypoglycaemic episodes (< 54 mg/dL) based on the post hoc analysis presented by the company for the dossier for this threshold value is very small compared to the patients with clinically significant hypoglycaemic episodes recorded in the study, which were recorded

solely on the basis of the PG value without the presence of symptoms. A possible explanation for the fact that the majority of patients did not develop any symptoms was discussed in the dossier assessment, namely that continuous monitoring by CGM was carried out in the study, so that countermeasures could already be taken in the event of hypoglycaemic alarm signals, which were recorded in the study above the threshold value of 70 mg/dL in CGM and subsequent self-measurement.

Following the oral hearing, the company subsequently submitted analyses on non-severe, confirmed symptomatic hypoglycaemic episodes (PG < 70 mg/dL) [2]. It is also striking for these analyses that the proportion of patients with at least one event for non-severe confirmed symptomatic hypoglycaemic episodes with PG < 70 mg/dL (4 vs. 6 patients, see supplementary information in Appendix A) is clearly smaller than that for non-severe hypoglycaemic episodes with PG < 70 mg/dL regardless of the presence of symptoms (288 vs. 289 patients, see information on hypoglycaemia alarm values in Table 19 in I Appendix C of the dossier assessment [1]). In its subsequent submission, the company states that although the symptoms of hypoglycaemic episodes in the ONWARDS 6 study were to be continuously recorded by investigators and patients in an electronic diary, the discrepancy between the results for the different operationalizations suggests that the recording of symptoms was possibly not fully followed up [2]. In the context of the discussion on non-severe hypoglycaemic episodes at the PG threshold value of 54 mg/dL, the company also pointed out in the oral hearing that the ONWARDS 6 study was an international study and that the symptoms were therefore not recorded to the extent required for an operationalization relevant to the benefit assessment [5].

As described above, non-severe confirmed hypoglycaemic episodes that were accompanied by symptoms are relevant for the benefit assessment, as only such events can be assumed to be patient-relevant events. However, the company's statements in the oral hearing and the information subsequently submitted after the hearing show that the company assumes that symptom recording in the ONWARDS 6 study may not have been fully followed up. However, if symptoms were incompletely recorded, it is possible that not all patient-relevant events were systematically recorded, so that the analyses on non-severe, confirmed hypoglycaemic episodes are not suitable for the benefit assessment, regardless of the threshold value used for confirmation.

However, for the dossier assessment it was assumed that the symptoms accompanying the hypoglycaemic episodes had been systematically and completely recorded as specified in the Case Report Form (CRF); therefore, the analyses on non-severe confirmed hypoglycaemic episodes pertaining to the threshold value 54 mg/dL were used. The fact that symptoms had possibly not been completely recorded was neither explained in the dossier nor was it addressed by the company in its comments [4], although the considerable discrepancy in the

number of patients with event with and without symptoms for the analyses on the PG score of 54 mg/dL had been explicitly discussed in the dossier assessment.

On the basis of the data subsequently submitted by the company after the oral hearing, it must be assumed that suitable data are lacking for both the outcome of non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL) and the outcome of non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 54 mg/dL), as both outcomes may have been influenced by the fact that symptoms recording was possibly not completely followed up [2,5]. The results on non-severe confirmed hypoglycaemic episodes (PG < 70 mg/dL) with potentially incomplete recording of the symptoms subsequently submitted by the company are presented as supplementary information in Appendix A.

The data on severe, confirmed hypoglycaemic episodes (PG < 54 mg/dL) with potentially incomplete recording of symptoms submitted by the company in the dossier are not used for the assessment due to the subsequently submitted information. Table 1 summarizes the results of the assessment, which are included in the overall conclusion on the extent of added benefit on the basis of the data subsequently submitted.

Table 1: Positive and negative effects from the assessment of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart

Positive effects	**Negative effects**
–	Serious/severe side effects ▪ serious hypoglycaemic episodes: hint of greater harm – extent: “minor”
No data are available for the outcomes of end-stage renal disease, diabetic retinopathies, health-related quality of life and non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL or PG < 70 mg/dL).	
PG: plasma glucose	

Overall, the fact that no suitable data are available for non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL or PG < 70 mg/dL) does not change the statement on added benefit.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion drawn in dossier assessment A24-90 on the added benefit of insulin icodec.

Table 2 below shows the result of the benefit assessment of insulin icodec, taking into account dossier assessment A24-90 and the present addendum.

Table 2: Insulin icodeca – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Adult patients with type 1 diabetes mellitus[c]	Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin degludec, insulin aspart, insulin glulisine, insulin lispro)[d]	Added benefit not proven

a. According to the SPC [6] , insulin icodec must be combined with bolus insulin in patients with type 1 diabetes mellitus in order to cover the insulin requirement at mealtimes.
b. Presentation of the ACT specified by the G-BA.
c. The ONWARDS 6 study only included patients who had been diagnosed with type 1 diabetes mellitus for at least 1 year and were receiving intensified conventional insulin therapy (ICT). It remains unclear whether the observed effects can be transferred to patients with newly diagnosed type 1 diabetes mellitus and to patients for whom conventional therapy (CT) or an insulin pump is an option. In the ONWARDS 6 study, insulin icodec was also only used in combination with insulin aspart, not with other bolus insulins. It remains unclear whether the observed results can be transferred to an application in combination with other bolus insulins.
d. The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus, if there is still the option of optimizing insulin therapy, does not correspond to an ACT.

ACT: appropriate comparator therapy; CT: conventional therapy; G-BA: Federal Joint Committee; ICT: intensified conventional insulin therapy

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Insulin icodec (Diabetes mellitus Typ 1); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2024 [Accessed: 02.12.2024]. URL: https://doi.org/10.60584/A24-90.

2. Novo Nordisk. Anhang zur Stellungnahme (Datennachreichung nach mündlicher Anhörung) zum IQWiG-Bericht Nr. 1892: Insulin icodec (Diabetes mellitus Typ 1); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1122/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Novo Nordisk. Insulin icodec; Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2024 [Accessed: 10.01.2025]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1122/#dossier.

4. Novo Nordisk. Stellungnahme zum IQWiG-Bericht Nr. 1892: Insulin icodec (Diabetes mellitus Typ 1); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1122/#beschluesse in the document "Zusammenfassende Dokumentation"].

5. Gemeinsamer Bundesausschuss. Insulin icodec (D-1085): mündliche Anhörung gemäß § 35 a Abs. 3 Satz 2 SGB V; stenografisches Wortprotokoll [online]. 2025 [Accessed: 10.01.2025]. URL: https://www.g-ba.de/downloads/91-1031-1122/2025-01-06_Wortprotokoll_Insulin-icodec_D-1085.pdf.

6. Novo Nordisk. Awiqli 700 Einheiten/ml Injektionslösung im Fertigpen [online]. 05.2024 [Accessed: 02.09.2024]. URL: https://www.fachinfo.de.

7. 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. https://doi.org/10.1016/0167-9473(94)90148-1.

Appendix A Supplementary information on non-severe, confirmed hypoglycaemic episodes

Table 3: Results (side effects) – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart

Study outcome category outcome	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]
ONWARDS 6					
Side effects					
Non-severe confirmed symptomatic[b] hypoglycaemic episodes					
PG < 70 mg/dL	290	4 (1.4)	292	6 (2.1)	0.67 [0.19; 2.35]; 0.564

a. Institute's calculation (unconditional exact test [CSZ method according to [7]).
b. According to the company, symptom recording may not have been followed up completely, although this was intended according to the CRF.

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; PG: plasma glucose; RCT: randomized controlled trial; RR: relative risk