IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Insulin degludec (Addendum to Commission A15-10)[1]

Addendum

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[1] Translation of addendum A15-26 *Insulin degludec* (*Addendum zum Auftrag A15-10*) (Version 1.1; Status: 7 August 2015). 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.

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[2] Due to legal data protection regulations, employees have the right not to be named.

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Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 13 July 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-10 (*Insulin degludec – Benefit assessment according to §35a SGB V*).

In its dossier [1], the pharmaceutical company (hereinafter referred to as "the company") only presented those analyses on the outcome "hyperglycaemia" from the NN1250-3561 study that included both symptomatic and non-symptomatic hyperglycaemic events. Hence for dossier assessment A15-10, no evaluable data were available for the patient-relevant outcome "symptomatic hyperglycaemia".

With its written comments, the company subsequently submitted data on symptomatic hyperglycaemia [2]. These were not interpretable because the data were not presented for the total population. After the oral hearing on insulin degludec, the company again submitted data on symptomatic hyperglycaemia [3,4]. The G-BA commissioned IQWiG to assess these data.

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

1.1 Changes in Version 1.1

The present Version 1.1 from 7 August 2015 replaces Version 1.0 of the Addendum from 29 July 2015. Compared with Version 1.0, Version 1.1 contains the following change: On page 4, the word "symptomatic" was deleted from the sentence "In the following Table 2, the total number of hyperglycaemic events is compared with the number of symptomatic hyperglycaemic events with missing ketone body measurement". In Table 2, the word "symptomatic" was deleted from the column heading "symptomatic hyperglycaemic events".

The result of the assessment was not affected by this change.

2 Assessment of the data submitted with the comment

In the framework of the commenting procedure on the early benefit assessment of insulin degludec, the company presented data on symptomatic hyperglycaemic events from the NN1250-3561 study. Besides symptomatic hyperglycaemic events with a plasma glucose level > 250 mg/dL, the company also presented a separate analysis for a subset of these symptomatic hyperglycaemic events with a plasma glucose level > 250 mg/dL, i.e. those events in which ketone bodies were additionally detected in the blood (> 1.5 mmol/L). The following Table 1 shows the data presented by the company. The results on ketoacidosis are additionally presented because ketoacidosis is a serious complication of symptomatic hyperglycaemia. The results on ketoacidosis were already available for the dossier assessment A15-10.

Table 1: Results on symptomatic hyperglycaemia – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

Study Outcome category Outcome Time point	Insulin degludec + insulin aspart N	Patients with events n (%)	Events n	Insulin detemir + insulin aspart N	Patients with events n (%)	Events n	Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart Effect estimate: RR [95% CI]; p-value/ rate ratio [95% CI]
NN1250-3561							
Morbidity							
Symptomatic hyperglycaemia							
Plasma glucose > 250 mg/dL							
26 weeks	174	116 (66.7)		175	117 (66.9)		1.00 [0.86; 1.16][a]; > 0.999[b]
			2612			3335	0.79 [0.52; 1.21]
52 weeks	174	132 (75.9)		175	129 (73.7)		1.03 [0.91; 1.16][a]; 0.683[b]
			4886			5788	0.78 [0.52; 1.18]
Plasma glucose > 200 mg/dL[c]							
26 weeks	174	ND	ND	175	ND	ND	ND
52 weeks	174	ND	ND	175	ND	ND	ND
Additional information: symptomatic hyperglycaemia (plasma glucose > 250 mg/dL) with ketosis (ketone bodies > 1.5 mmol/L)							
26 weeks	174	8 (4.6)		175	15 (8.6)		0.54 [0.23; 1.24]; 0.141[b]
			11			32	0.28 [0.09; 0.81]
52 weeks	174	13 (7.5)		175	19 (10.9)		0.69 [0.35; 1.36]; 0.288[b]
			28			65	0.21 [0.08; 0.55]
Ketoacidosis							
26 weeks	174	0 (0)		175	0 (0)		NC; > 0.999
			0			0	ND
52 weeks	174	2 (1.1)		175	0 (0)		5.03 [0.24; 103.99][a, d]; 0.169[b]
			2			0	ND

a: Institute's calculation (asymptotic).
b: Institute's calculation, unconditional exact test (CSZ method [5]).
c: In the dossier, the company had also presented analyses on hyperglycaemic events with a plasma glucose level > 200 mg/dL. In the commenting procedure, the company presented no analyses on symptomatic hyperglycaemic events with this threshold value.
d: Correction factor 0.5.

CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of patients in the analysis; n: absolute number; NC: not calculated; ND: no data; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Symptomatic hyperglycaemia

The risk of bias for the outcome "symptomatic hyperglycaemia" was rated as high both in the main and in the extension study due to the subjective component in an open-label study design.

No statistically significant difference between the treatment groups was shown for the outcome "symptomatic hyperglycaemia with a plasma glucose level > 250 mg/dL". No analyses were available for the outcome "symptomatic hyperglycaemia with a plasma glucose level > 200 mg/dL".

Overall, there was no hint of an added benefit of insulin degludec in comparison with insulin detemir; an added benefit for the outcome "symptomatic hyperglycaemia" is therefore not proven.

No results on effect modifications that were constant for 26 and 52 weeks were shown in the data on subgroups additionally presented by the company.

Outcome additionally presented: symptomatic hyperglycaemia with ketosis

Besides analyses on all symptomatic hyperglycaemic events, the company also presented analyses on the subset of symptomatic hyperglycaemic events with detection of ketone bodies. The company argued that these events were particularly relevant because in these cases, the risk of ketoacidosis was increased because of the detection of ketone bodies. However, the result of the NN1250-3561 study itself contradicts this argument because symptomatic hyperglycaemia with ketosis was detected in a higher number of patients under insulin degludec, but a higher number of ketoacidosis actually occurred in these patients. Overall, there was no proof that the operationalization on symptomatic hyperglycaemia with ketosis presented by the company is suitable to delineate events of particular relevance.

Irrespective of this, the results on symptomatic hyperglycaemia with ketosis of the NN1250-3561 study cannot be finally interpreted. In the NN1250-3561 study, the patients had to measure their level of ketone bodies in the blood in every hyperglycaemic event with a plasma glucose level of > 250 mg/dL. In the following Table 2, the total number of hyperglycaemic events is compared with the number of hyperglycaemic events with missing ketone body measurement.

Table 2: Measurement of ketone bodies in the NN1250-3561 study

Study	Hyperglycaemia		
Time point Group	N	Number of events (total) n	Number of events (without measurement of ketone bodies) n (%)
NN1250-3561			
26 weeks			
Insulin degludec[a]	174	18 209	3125 (17.2)
Insulin detemir[a]	175	17 698	3252 (18.4)
52 weeks			
Insulin degludec[a]	174	33 689	5541 (16.4)
Insulin detemir[a]	174	29 627	4847 (16.3)

a: In each case plus insulin aspart.
N: number of patients in the analysis, n: number of events; RCT: randomized controlled trial

A total of 63 316 hyperglycaemic events with a plasma glucose level of > 250 mg/dL occurred in the NN1250-3561 study. Despite the specification in the protocol, no such measurements were conducted in more than 10 000 events (5541 under insulin degludec and 4847 under insulin detemir, in each case just over 16%). In comparison, there were only 93 symptomatic events with detection of ketone bodies (28 under insulin degludec and 65 under insulin detemir) (see Table 1). Because of this and because of the risk of bias that was high anyway (outcome with subjective component in open-label study), the results on the outcome "symptomatic hyperglycaemia with ketosis" cannot be finally interpreted.

Summary

No proof of added benefit of insulin degludec in comparison with the appropriate comparator therapy results from the data on symptomatic hyperglycaemia subsequently submitted by the company. Overall, the data subsequently submitted did not change the assessment of the benefit assessment A15-10 [6]: For girls with type 1 diabetes mellitus, there is a hint of a lesser benefit of insulin degludec in comparison with the appropriate comparator therapy. The added benefit of insulin degludec versus the appropriate comparator therapy for boys with type 1 diabetes mellitus is not proven.

3 References

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2. Novo Nordisk. NN1250-exploratory: clinical trial report [unpublished]. 19 June 2015.

3. Novo Nordisk. NN1250-exploratory: clinical trial report [unpublished]. 8 July 2015.

4. Novo Nordisk. Nachtrag zur mündlichen Anhörung vom 07. Juli 2015 zur Nutzenbewertung von Insulin degludec 2015-03-01-D-158 [unpublished]. 2015.

5. 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.

6. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Insulin degludec (neues Anwendungsgebiet): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-10 [online]. 28 May 2015 [accessed: 3 June 2015]. (IQWiG-Berichte; Volume 306). URL: https://www.iqwig.de/download/A15-10_Insulin-degludec-neues-Anwendungsgebiet_Nutzenbewertung-35a-SGB-V.pdf.