

IQWiG Reports – Commission No. A15-30

**Insulin degludec/liraglutide
(new therapeutic indication) –
Benefit assessment according to
§35a Social Code Book V¹**

Extract

¹ Translation of Sections 2.1 to 2.6 of the dossier assessment *Insulin degludec/Liraglutid (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11. November 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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³ Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP-1	glucagon-like peptide 1
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OAD	oral antidiabetic
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TI	therapeutic indication

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination insulin degludec/liraglutide (new therapeutic indication). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 5 August 2015.

Research question

The aim of this report was to assess the added benefit of the fixed combination of insulin degludec/liraglutide in combination with oral antidiabetics (OADs) in comparison with metformin + human insulin as appropriate comparator therapy (ACT) in adult patients with type 2 diabetes mellitus when OADs combined with a glucagon-like peptide 1 (GLP-1) receptor agonist do not provide adequate glycaemic control. For patients for whom metformin is unsuitable according to the Summary of Product Characteristics (SPC), human insulin constitutes the ACT.

Results

The company identified no relevant study for a direct comparison between insulin degludec/liraglutide and the ACT.

In its information retrieval, the company identified one randomized controlled trial (RCT) (NN9068-3851, study DUAL III), in which insulin degludec/liraglutide was compared with continued ongoing treatment with a GLP-1 receptor agonist. The study was conducted in the subindication “metformin suitable according to the SPC”, for which human insulin + metformin constitutes the ACT. The DUAL III study was therefore potentially suitable for an indirect comparison in this subindication. The company had also searched for studies on the ACT for an indirect comparison, but stated that it had identified no relevant study. The company argued that the potentially relevant studies it had identified were not sufficiently similar to the DUAL III studies with regard to content. However, the information provided by the company was insufficient with regard to content and could therefore not be verified. Moreover, the company’s search was unsuitable to completely identify the potentially relevant studies. Hence it remains unclear whether an indirect comparison would have been possible.

In summary, the company presented no relevant data in its dossier for the assessment of the added benefit of insulin degludec/liraglutide in combination with OADs versus the ACT in patients in whom OADs in combination with a GLP-1 receptor agonist do not provide adequate glycaemic control. Hence there was no hint of an added benefit of insulin degludec/

liraglutide in combination with OADs in comparison with the ACT; an added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

Since no relevant data were presented for the benefit assessment of insulin degludec/liraglutide in combination with OADs in patients in whom OADs in combination with a GLP-1 receptor agonist do not provide adequate glycaemic control, an added benefit versus the ACT specified by the G-BA is not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

Table 2 presents a summary of the extent and probability of the added benefit of insulin degludec/liraglutide.

Table 2: Insulin degludec/liraglutide – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy	Extent and probability of added benefit
Combination with oral antidiabetics: <ul style="list-style-type: none"> ▪ when oral antidiabetics in combination with a GLP-1 receptor agonist do not provide adequate glycaemic control 	Metformin + human insulin <i>(Note: If metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option.)</i>	Added benefit not proven
GLP-1: glucagon-like peptide 1		

This result concurs with the company's assessment, which also derived no added benefit for insulin degludec/liraglutide in combination with OADs. The G-BA decides on the added benefit.

⁴ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

2.2 Research question

The aim of this report was to assess the added benefit of the fixed combination of insulin degludec/liraglutide in combination with OADs in comparison with metformin + human insulin as ACT in adult patients with type 2 diabetes mellitus when OADs combined with a GLP-1 receptor agonist do not provide adequate glycaemic control.

The G-BA specified human insulin + metformin as ACT for the present therapeutic indication, noting that only human insulin constitutes the ACT when metformin is in-appropriate according to the SPC.

The company concurred with this specification.

The company also stated that, besides human insulin, insulin analogues were used as ACT for outcomes of a short-term treatment. The available evidence on longterm data supports human insulin as ACT. No general transferability of the results of studies with insulin analogues to human insulin can be assumed because there is a lack of data on late complications. On the basis of the IQWiG assessment [3], transferability can be assumed for the 2 insulin analogues insulin detemir and insulin glargine for other outcomes, however.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on insulin degludec/liraglutide (status: 15 July 2015)
- bibliographical literature search on insulin degludec/liraglutide (last search on 2 June 2015)
- search in trial registries for studies on insulin degludec/liraglutide (last search on 3 June 2015)
- bibliographical literature search on the ACT (last search on 18 May 2015)
- search in trial registries for studies on the ACT (last search on 16 July 2015)

To check the completeness of the study pool:

- search in trial registries for studies on insulin degludec/liraglutide (last search on 14 August 2015)

The company identified no relevant study for a direct comparison between insulin degludec/liraglutide and the ACT. No relevant study of direct comparison was identified from the check of completeness.

When no studies of direct comparisons versus the ACT are available, it is possible to investigate the added benefit on the basis of indirect comparisons. In the steps of information retrieval mentioned, the company identified one RCT (NN9068-3851, study DUAL III), in which insulin degludec/liraglutide was compared with continued ongoing treatment with a GLP-1 receptor agonist. The study was conducted in the subindication “metformin suitable according to the SPC”, for which human insulin + metformin constitutes the ACT. The DUAL III study was therefore potentially suitable for an indirect comparison in this subindication. The company had also searched for studies on the ACT for an indirect comparison, but stated that it had identified no relevant study. The company argued that the potentially relevant studies it had identified were not sufficiently similar to the DUAL III studies with regard to content. However, the information provided by the company was insufficient with regard to content and could therefore not be verified. Moreover, the company’s search was unsuitable to completely identify the potentially relevant studies. Hence it remains unclear whether an indirect comparison would have been possible (see Sections 2.7.2.1 and 2.7.2.2 of the full dossier assessment).

The company also presented no further documents (non-randomized comparative studies or further investigations) to investigate the added benefit of insulin degludec/liraglutide in combination with OADs.

In summary, the company presented no studies in its dossier that are suitable to investigate the added benefit of insulin degludec/liraglutide in comparison with the ACT.

2.4 Results on added benefit

The company presented no relevant data in its dossier for the assessment of the added benefit of insulin degludec/liraglutide in combination with OADs versus the ACT in patients in whom OADs in combination with a GLP-1 receptor agonist do not provide adequate glycaemic control. Hence there was no hint of an added benefit of insulin degludec/liraglutide in combination with OADs in comparison with the ACT; an added benefit is therefore not proven.

2.5 Extent and probability of added benefit

Since no relevant data were presented for the benefit assessment of insulin degludec/liraglutide in combination with OADs in patients in whom OADs in combination with a GLP-1 receptor agonist do not provide adequate glycaemic control, an added benefit versus the ACT (metformin + human insulin) specified by the G-BA is not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

Table 3: Insulin degludec/liraglutide – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy	Extent and probability of added benefit
Combination with oral antidiabetics: <ul style="list-style-type: none"> ▪ when oral antidiabetics in combination with a GLP-1 receptor agonist do not provide adequate glycaemic control 	Metformin + human insulin <i>(Note: If metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option.)</i>	Added benefit not proven
GLP-1: glucagon-like peptide 1		

This result concurs with the company's assessment, which also derived no added benefit for insulin degludec/liraglutide in combination with OADs.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as no relevant data for the benefit assessment were presented.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22 April 2015 [accessed: 20 October 2015]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

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3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Langwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 2: Abschlussbericht; Auftrag A05-03; Version 1.1 [online]. 26 February 2009 [accessed: 24 August 2015]. (IQWiG-Berichte; Volume 42). URL: http://www.iqwig.de/download/A05-03_Abschlussbericht_Langwirksame_Insulinanaloga_bei_Diabetes_mellitus_Typ_2_V1.1.pdf.

The full report (German version) is published under <https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-30-insulin-degludec/liraglutid-neues-anwendungsgebiet-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6905.html>.