IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Insulin degludec – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Assessment module I, Sections I 2.1 to I 2.6, and Assessment module II, Sections II 2.1 to II 2.6, of the dossier assessment *Insulin degludec – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 July 2014). 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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Insulin degludec

Assessment module I

Type 1 diabetes mellitus

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IQWiG thanks the medical and scientific advisor for his contribution to the assessment. However, the advisor was not involved in the actual preparation of the assessment. The responsibility for the contents of the assessment lies solely with IQWiG.

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Keywords: insulin degludec, diabetes mellitus - type 1, benefit assessment

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 2 Benefit assessment

I 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 insulin degludec. 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 29 April 2014.

In addition to the information provided in Modules 1 to 4, it was necessary to use information from Module 5 of the company's dossier for the present benefit assessment. This was information on study methods and study results. However, the company objected to the use and publication of this information and hence did not provide the complete necessary information on study methods and study results for publication.

Research question

The drug insulin degludec is approved for several therapeutic indications. The aim of this assessment module was to assess the added benefit of insulin degludec in combination with short-/rapid-acting insulin compared with the appropriate comparator therapy (ACT) in adult patients with type 1 diabetes mellitus.

The benefit assessment of insulin degludec in combination with bolus insulin in type 1 diabetes mellitus was conducted in comparison with the ACT human insulin specified by the G-BA.

This deviated from the company's approach, which specified insulin analogues as comparator therapy without providing sufficient justification for this approach. However, the company also searched for studies with human insulin. The transferability of the results of the studies with insulin analogues used by the company was viewed to be sufficient for the present research question. Hence this deviation had no consequences for the benefit assessment.

The assessment was based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) with a minimum study duration of 24 weeks were included in the assessment.

Results

The studies NN1250-3583, NN1250-3770 and NN1250-3585 were identified as being relevant for this benefit assessment. However, the company did not include the NN1250-3585 study in the assessment. The study pool presented by the company for the therapeutic indication type 1 diabetes mellitus is therefore incomplete.

Moreover, the company did not provide all necessary information in the Modules 1 to 4 and objected to the use of information from Module 5. Hence the added benefit of insulin degludec in patients with type 1 diabetes mellitus is not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[2]

On the basis of the results presented, the extent and probability of the added benefit of the drug insulin degludec compared with the ACT for the therapeutic indication type 1 diabetes mellitus is assessed as follows:

Table 1: Insulin degludec (type 1 diabetes mellitus): extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy	Extent and probability of added benefit
Type 1 diabetes mellitus	Human insulin	Added benefit not proven

The G-BA decides on the added benefit.

[2] 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), see [1]. 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), see [2].

I 2.2 Research question

The drug insulin degludec is approved for several therapeutic indications. The aim of this assessment module was to assess the added benefit of insulin degludec in combination with short-/rapid-acting insulin compared with the ACT in adult patients with type 1 diabetes mellitus.

The benefit assessment of insulin degludec in combination with bolus insulin in type 1 diabetes mellitus was conducted in comparison with the ACT human insulin specified by the G-BA.

This deviated from the company's approach, which specified insulin analogues as comparator therapy without providing sufficient justification for this approach. However, the company also searched for studies with human insulin. The transferability of the results of the studies with insulin analogues used by the company was viewed to be sufficient for the present research question. Hence this deviation had no consequences for the benefit assessment.

The assessment was based on patient-relevant outcomes. Direct comparative RCTs with a minimum study duration of 24 weeks were included in the assessment.

Further information about the research question can be found in Module 3D, Section 3.1, and Module 4D, Section 4.2.1 of the dossier, and in Sections I 2.7.1 and I 2.7.2.1 of the full dossier assessment.

I 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 (studies completed up to 26 February 2014)
- bibliographical literature search on insulin degludec (last search on 26 February 2014)
- search in trial registries for studies on insulin degludec (last search on 26 February 2014)

From the steps of information retrieval mentioned, the studies NN1250-3583, NN1250-3770 and NN1250-3585 were identified as being relevant for this benefit assessment. However, the company did not include the NN1250-3585 study in the assessment.

Hence the study pool presented by the company was incomplete. Table 2 shows the relevant studies.

Table 2: Study pool – RCT, direct comparison: insulin degludec + insulin aspart vs. human insulin/insulin analogues (long-acting + short-acting)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Insulin degludec + insulin aspart vs. insulin glargine + insulin aspart			
NN1250-3583 (with the NN1250-3644 extension study)	Yes	Yes	No
NN1250-3770	Yes	Yes	No
Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart			
NN1250-3585 (with the NN1250-3725 extension study)	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The company named the NN1250-3585 study in its study list (Module 4D, Table 4-7). In Table 4-8 in Module 4D however, "violates inclusion criterion insulin glargine in combination with short-acting insulin" was provided as reason for exclusion. However, this reason for exclusion is not comprehensible and not reasonable for the present benefit assessment, and the company contradicts its own inclusion and exclusion criteria with the exclusion (see Section I 2.2).

The company did not provide a reason for this approach. The company already provided information both on insulin glargine and on insulin detemir in its specification of the ACT so that no rationale for the exclusion of the NN1250-3585 study with insulin detemir was detectable there either.

Table 3 describes the study characteristics of the relevant studies.

Table 3: Characteristics of the studies on the present research question – RCT, direct comparison: insulin degludec + insulin aspart vs. human insulin/insulin analogues (long-acting + short-acting)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome[a]
Insulin degludec + insulin aspart vs. insulin glargine + insulin aspart						
NN1250-3583	RCT, open-label, parallel, multicentre, treat-to-target	Adult patients with type 1 diabetes mellitus	IDeg + IAsp (N = 472) IGlar +IAsp (N = 157)	Treatment phase: 52 weeks Follow-up: 1 week NN1250-3644 extension study: 52 weeks Follow-up: 1 week	79 centres in Europe, Russia, South Africa, United States 09/2009-11/2010	Primary outcome: HbA1c change from baseline to week 52
NN1250-3770	RCT, open-label, parallel, multicentre, treat-to-target	Adult patients with type 1 diabetes mellitus	IDeg Flex + IAsp (N = 164)[b] IDeg + IAsp (N = 165) IGlar + IAsp (N = 164)	Treatment phase: 26 weeks Follow-up: 1 week NN1250-3770-ext extension study[c]: 26 weeks Follow-up: 1 week	71 centres in Europe and United States 03/2010-11/2010	Primary outcome: HbA1c change from baseline to week 26
Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart						
NN1250-3585	RCT, open-label, parallel, multicentre, treat-to-target	Adult patients with type 1 diabetes mellitus	IDeg + IAsp (N = 303) IDet + IAsp (N = 153)	Treatment phase: 26 weeks Follow-up: 1 week NN1250-3725 extension study: 26 weeks Follow-up: 1 week	Europe, India, Japan, Southeast Asia	Primary outcome: HbA1c change from baseline to week 26

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment.
b: The flexible administration of insulin degludec in this arm does not concur with the German approval.
c: In the extension phase, the patients of the insulin degludec arm with fixed injection times were switched to the flexible administration of insulin degludec, which is not compliant with the approval.

HbA1c: glycosylated haemoglobin A1c; IAsp: insulin aspart; IDeg: insulin degludec; IDet: insulin detemir; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

All studies were randomized, open-label, treat-to-target studies conducted in several centres including Europe. Each of the studies included adult patients with type 1 diabetes mellitus. The treatment phase of the 3 studies was at least 26 weeks (52 weeks in the NN1250-3583 study included by the company), followed by a 1-week follow-up phase. Insulin aspart was used before each meal as bolus insulin in all studies. All studies aimed at a fasting plasma glucose level of < 5 mmol/L (90 mg/dL) as treatment goal. All studies were designed to investigate the change in HbA1c from baseline to the end of treatment and are therefore comparable in their goal [3]. Hence there are no indications that the NN1250-3585 study is not relevant for the present assessment. Moreover, the number of randomized patients in the NN1250-3585 study (N = 456) was regarded to be sufficiently high to influence the results in the framework of the benefit assessment to a potentially relevant degree in comparison with the studies NN1250-3583 and NN1250-3770 (N = 958 in the relevant study arms).

Overall, the study pool compiled by the company was incomplete, and the study results presented by the company were not evaluable for this reason already.

Use of information from Module 5

It should be pointed out that the dossier (Module 1 to 4) on insulin degludec in the therapeutic indication of type 1 diabetes mellitus, which is to be published, also does not contain all information on the studies NN1250-3583 and NN1250-3770, on which the benefit assessment is based. The company objected to the use of data from Module 5. Due to this objection, no dossier assessment based on complete data could have been conducted even if the company had included the NN1250-3585 study in its assessment.

In addition to the information on the relevance of the NN1250-3585 study, according to the European Public Assessment Report (EPAR), the studies NN1250-3583, NN1250-3770 and NN1250-3585 were each followed by an extension phase of the primary treatment phase: study NN1250-3644 (extension of the NN1250-3583 study), study NN1250-3770-ext (extension of the NN1250-3770 study) and study NN1250-3725 (extension of the NN1250-3585 study) [3]. The company excluded these studies with the justification that these were no RCTs. The NN1250-3770-ext extension study is not relevant for the present benefit assessment because the patients of the insulin degludec arm (with fixed injection times) were switched to the flexible administration of insulin degludec, which is not compliant with the approval. In contrast, it is not clear from the available documents that the 2 extension studies NN1250-3644 and NN1250-3725 are not relevant. On the contrary, the information provided in Module 4D, for example, suggests for the NN1250-3644 extension study that a sufficient number of patients continued the study in the extension phase under randomized conditions.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4D, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections I 2.7.2.1 and I 2.7.2.3 of the full dossier assessment.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4D, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections I 2.7.2.3.1 and I 2.7.2.3.2 of the full dossier assessment.

I 2.4 Results on added benefit

The study pool presented by the company for the therapeutic indication type 1 diabetes mellitus was incomplete. Moreover, the company did not provide all necessary information in the Modules 1 to 4 and objected to the use of information from Module 5. Hence the added benefit of insulin degludec in patients with type 1 diabetes mellitus is not proven.

This result deviates from that of the company, which derived an indication of an added benefit of insulin degludec in the therapeutic indication type 1 diabetes mellitus.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4D, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier.

I 2.5 Extent and probability of added benefit

No proof of added benefit of insulin degludec in the therapeutic indication type 1 diabetes mellitus in comparison with the ACT specified by the G-BA could be derived from the data presented. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

This assessment deviates from that of the company, which derived an indication of considerable added benefit for insulin degludec in combination with short-/rapid-acting insulin in patients with type 1 diabetes mellitus.

The G-BA decides on the added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4D, Section 4.4 of the dossier, and in Section I 2.7.2.8 of the full dossier assessment.

I 2.6 List of included studies

Not applicable as the company presented an incomplete study pool in its dossier and objected to the use of information from Module 5.

References for English extract

Please see full assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 7 February 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. European Medicines Agency. Tresiba: European public assessment report [online]. 20 September 2012 [accessed: 5 May 2014]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002498/WC500139010.pdf.

Insulin degludec

Assessment module II

Type 2 diabetes mellitus

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IQWiG thanks the medical and scientific advisor for his contribution to the assessment. However, the advisor was not involved in the actual preparation of the assessment. The responsibility for the contents of the assessment lies solely with IQWiG.

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Keywords: insulin degludec, diabetes mellitus – type 2, benefit assessment

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
DPP-4	dipeptidyl peptidase 4
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OAD	oral antidiabetics
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

II 2 Benefit assessment

II 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 insulin degludec. 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 29 April 2014.

In addition to the information provided in Modules 1 to 4, it was necessary to use information from Module 5 of the company's dossier for the present benefit assessment. This was information on study methods and study results. However, the company objected to the use and publication of this information and hence did not provide the complete necessary information on study methods and study results for publication.

Research question

The aim of assessment module II was to assess the added benefit of insulin degludec for the treatment of adults with type 2 diabetes mellitus in monotherapy, in combination with oral antidiabetics (OAD) and in combination with bolus insulin.

The assessment was conducted separately for 3 subindications versus the appropriate comparator therapy (ACT) specified by the G-BA.

Table 1: Research questions, subindications and ACTs on insulin degludec in type 2 diabetes mellitus considered in assessment module II

Research question[a]	Subindication	ACT specified by the G-BA
A	Insulin degludec monotherapy	Human insulin
B	Insulin degludec + OAD[b]	Human insulin + metformin (Note: If metformin is inappropriate according to the SPC, human insulin is to be used as treatment option.)
C	Insulin degludec + bolus insulin ± OAD	Human insulin ± metformin[c]

a: Designation corresponds to the coding in the company's dossier.
b: The G-BA's commission referred to the combination of insulin degludec with one or several other antidiabetics (except insulin). According to the approval status valid at the time point of the submission of the dossier, this subindication was limited to the combination of insulin degludec with OAD in analogy to the company's approach.
c: In combination with bolus insulin (without OAD) in the framework of intensified conventional insulin treatment, additional administration of metformin is not generally indicated.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetics; SPC: Summary of Product Characteristics

For all 3 subindications (**research questions A, B and C**), the company deviated from the ACT specified by the G-BA with regard to the insulin component and specified insulin analogues instead of human insulin without providing sufficient justification for this approach. However, the company also searched for studies with human insulin. The transferability of the results of the studies with insulin analogues used by the company was viewed to be sufficient for the present research question. Hence this deviation had no consequences for the benefit assessment.

For the subindication insulin degludec + OAD and insulin degludec + bolus insulin ± OAD (**research questions B and C**), the company also deviated from the ACT with regard to the OAD component and specified any OAD (also combinations of several drugs) instead of metformin without providing sufficient justification for this approach.

The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs) with a minimum duration of 24 weeks.

Results

Research question A: insulin degludec monotherapy

The company identified the NN1250-3668 study for research question A. However, the company did not use this study for deriving an added benefit because, from the company's point of view, the proportion of the relevant subpopulation was too small. The company presented no analyses for the relevant subpopulation. No relevant analyses on the study results of the NN1250-3668 study were available for the present benefit assessment.

Overall the added benefit of insulin degludec in monotherapy versus the ACT specified by the G-BA is not proven.

Research question B: insulin degludec + OAD

The company used the studies NN1250-3579, NN1250-3586, NN1250-3668 and NN1250-3672 on the basis of the respective total populations for the assessment of research question B. For the present benefit assessment, only subpopulations were relevant for all 4 studies.

For the studies NN1250-3579 and NN1250-3672 however, over 80% of the included patients corresponded to the relevant subpopulation. Hence for both studies it would have been possible to assess the added benefit of insulin degludec on the basis of the respective total populations if the company had provided the complete necessary information on study methods and study results. For the studies NN1250-3586 and NN1250-3668, the proportion of patients corresponding to the relevant subpopulation was far below 80% in each case. Hence the results for the total populations could not be used for the assessment of the added benefit of insulin degludec, but only the results of the respective relevant subpopulations. The company did not provide these data.

Moreover, the company listed the NN1250-3643 extension study for the NN1250-3579 study in the table of the resulting study pool, but did not include it in its assessment. It was not clear from the available documents that the study was not relevant. On the contrary, the information provided in Module 4B suggests that a sufficient number of patients continued the study in the extension phase under randomized conditions.

Overall the added benefit of insulin degludec + OAD versus the ACT specified by the G-BA is not proven.

Research question C: insulin degludec + bolus insulin ± OAD

The company used the NN1250-3582 study for the assessment of research question C. Only a subpopulation of this study was relevant for the present research question, but over 80% of the patients included corresponded to the relevant subpopulation. Hence it would have been possible to assess the added benefit of insulin degludec on the basis of the total population if the company had provided the complete necessary information on study methods and study results for publication.

Moreover, the company listed the NN1250-3667 extension study of the NN1250-3582 study in the table of the resulting study pool, but did not include it in its assessment. It was not clear from the available documents that the study was not relevant. On the contrary, the information provided in Module 4B suggests that a sufficient number of patients continued the study in the extension phase under randomized conditions.

Overall the added benefit of insulin degludec + bolus insulin ± OAD versus the ACT specified by the G-BA is not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[2]

On the basis of the results presented, the extent and probability of the added benefit of the drug insulin degludec compared with the ACT for the therapeutic indication type 2 diabetes mellitus is assessed as follows:

[2] 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), see [1]. 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), see [2].

Table 2: Insulin degludec (type 2 diabetes mellitus): extent and probability of added benefit

Research question[a]	**Subindication**	**ACT**	**Extent and probability of added benefit**
A	Insulin degludec monotherapy	Human insulin	Added benefit not proven
B	Insulin degludec + OAD[b]	Human insulin + metformin (Note: If metformin is inappropriate according to the SPC, human insulin is to be used as treatment option.)	Added benefit not proven
C	Insulin degludec + bolus insulin ± OAD	Human insulin ± metformin[c]	Added benefit not proven

a: Designation corresponds to the coding in the company's dossier.
b: The specification of the G-BA's ACT referred to the combination of insulin degludec with one or several other antidiabetics (except insulin). According to the approval status valid at the time point of the submission of the dossier, this subindication was limited to the combination of insulin degludec with OAD in analogy to the company's approach.
c: In combination with bolus insulin (without OAD) in the framework of intensified conventional insulin treatment, additional administration of metformin is not generally indicated.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetics; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

II 2.2 Research questions

The aim of assessment module II was to assess the added benefit of insulin degludec for the treatment of adults with type 2 diabetes mellitus in monotherapy, in combination with OAD and in combination with bolus insulin.

Following the company's research questions in the dossier, the assessment was conducted separately for 3 subindications versus the ACT specified by the G-BA. These are presented in Table 3.

Table 3: Research questions, subindications and ACTs on insulin degludec in type 2 diabetes mellitus considered in assessment module II

Research question[a]	Subindication	ACT specified by the G-BA
A	Insulin degludec monotherapy	Human insulin
B	Insulin degludec + OAD[b]	Human insulin + metformin (Note: If metformin is inappropriate according to the SPC, human insulin is to be used as treatment option.)
C	Insulin degludec + bolus insulin ± OAD	Human insulin ± metformin[c]

a: Designation corresponds to the coding in the company's dossier.
b: The specification of the G-BA's ACT referred to the combination of insulin degludec with one or several other antidiabetics (except insulin). According to the approval status valid at the time point of the submission of the dossier, this subindication was limited to the combination of insulin degludec with OAD in analogy to the company's approach.
c: In combination with bolus insulin (without OAD) in the framework of intensified conventional insulin treatment, additional administration of metformin is not generally indicated.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetics; SPC: Summary of Product Characteristics

For all 3 subindications (**research questions A, B and C**), the company deviated from the ACT specified by the G-BA with regard to the insulin component and specified insulin analogues instead of human insulin without providing sufficient justification for this approach. However, the company also searched for studies with human insulin. The transferability of the results of the studies with insulin analogues used by the company was viewed to be sufficient for the present research question. Hence this deviation had no consequences for the benefit assessment.

For the subindication insulin degludec + OAD and insulin degludec + bolus insulin ± OAD (**research questions B and C**), the company also deviated from the ACT with regard to the OAD component and specified any OAD (also combinations of several drugs) instead of metformin without providing sufficient justification for this approach.

For **research question B** (insulin degludec + OAD), the specification of the G-BA's ACT also referred to the combination of insulin degludec with other antidiabetics such as glucagon-like peptide 1 agonists. According to the approval valid for the assessment (status May 2013),

insulin degludec was not approved for this combination. In the present assessment, the research question is therefore limited to the combination with OAD. This concurs with the company's approach.

The assessment was conducted based on patient-relevant outcomes and on RCTs with a minimum duration of 24 weeks.

Further information about the research questions can be found in Modules 3A-C, Sections 3.1, and in Modules 4A-C, Sections 4.2.1, of the dossier, and in Sections II 2.7.1, II 2.7.2, II 2.7.3.2.1 and II 2.7.4.2.1 of the full dossier assessment.

II 2.3 Research question A: insulin degludec monotherapy

II 2.3.1 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 (studies completed up to 3 March 2014)
- bibliographical literature search on insulin degludec (last search on 17 February 2014)
- search in trial registries for studies on insulin degludec (last search on 19 February 2014)

To check the completeness of the study pool:

- bibliographical literature search on insulin degludec (last search on 16 May 2014)
- search in trial registries for studies on insulin degludec (last search on 10 June 2014)

This check produced no deviations from the study pool presented in the dossier.

The company identified the NN1250-3668 study for the research question on insulin degludec in monotherapy. According to the information provided in Module 4A, only 21 of the 687 (approximately 3%) patients included corresponded to the target population. As this proportion was too small from the company's point of view, the company presented no results of this study apart from the study characteristics. The company presented no analyses for the relevant subpopulation. The company objected to the use of data from Module 5, which is not to be published, for the present benefit assessment (see Section II 2.2).

Overall no relevant analyses on the study results of the NN1250-3668 study were available.

Further information on the inclusion criteria for studies in this benefit assessment, the methods and results of information retrieval and the study pool resulting from it can be found in Module 4A, Sections 4.2.2, 4.2.3 and 4.3.1.1 of the dossier, and in Section II 2.7.2 of the full dossier assessment.

II 2.3.2 Results on added benefit

No relevant data were available for the research question on insulin degludec in monotherapy. Hence the added benefit of insulin degludec in monotherapy in type 2 diabetes mellitus versus the ACT specified by the G-BA is not proven.

II 2.3.3 Extent and probability of added benefit

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of insulin degludec in monotherapy for the treatment of type 2 diabetes mellitus in comparison with the ACT specified by the G-BA (human insulin). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. The company also claimed no added benefit for this research question.

Further information about the extent and probability of the added benefit can be found in Module 4A, Section 4.4 of the dossier, and in Section II 2.7.2 of the full dossier assessment.

II 2.4 Research question B: insulin degludec + OAD

II 2.4.1 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 (studies completed up to 3 March 2014)
- bibliographical literature search on insulin degludec (last search on 17 February 2014)
- search in trial registries for studies on insulin degludec (last search on 19 February 2014)

To check the completeness of the study pool:

- bibliographical literature search on insulin degludec (last search on 16 May 2014)
- search in trial registries for studies on insulin degludec (last search on 10 June 2014)

The studies identified from the steps of information retrieval mentioned that are relevant for the assessment of research question B are presented in Table 4.

Table 4: Study pool – RCT, direct comparison: insulin degludec + OAD vs. human insulin/insulin analogues + metformin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
NN1250-3579[b] (with the NN1250-3643 extension study)	Yes	Yes	No
NN1250-3672[b]	Yes	Yes	No
NN1250-3586[c]	Yes	Yes	No
NN1250-3668[c]	Yes	Yes	No

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
b: Over 80% of the patients included corresponded to the relevant subpopulation.
c: No more than 11% (NN1250-3586), and no more than 35.6% (NN1250-3668, referring to the 2 relevant treatment arms) of the patients included corresponded to the relevant subpopulation.
OAD: oral antidiabetics; RCT: randomized controlled trial; vs.: versus

The 4 studies NN1250-3579 (with the NN1250-3643 extension study), NN1250-3586, NN1250-3668 and NN1250-3672 were identified. For all 4 studies, only subpopulations were relevant. However, no analyses for these relevant subpopulations were available in Module 4B of the dossier.

For the studies NN1250-3579 and NN1250-3672 however, over 80% of the included patients corresponded to the relevant subpopulation. Hence for both studies it would have been possible to assess the added benefit of insulin degludec on the basis of the respective total populations if the company had provided the complete necessary information on study methods and study results (see Section II 2.4.2). The study characteristics are presented in Section II 2.4.1.1.

For the studies NN1250-3586 and NN1250-3668, the proportion of patients corresponding to the relevant subpopulation was far below 80% in each case (study NN1250-3586: 11.0% maximum; study NN1250-3668: 35.6% maximum). Hence the results for the total populations could not be used for the assessment of the added benefit of insulin degludec. If one considers the number of the respective patients corresponding to the relevant subpopulation across all 4 studies (approximately 1471 patients), these 2 studies with a maximum of 203 patients (approximately 15%) constitute a comparably small proportion. The influence of these results on the overall conclusion of the added benefit in case of the assessment of the study results of the studies NN1250-3579 and NN1250-3672 would have to be considered negligible. Hence there is no detailed presentation of the study characteristics of the studies NN1250-3586 and NN1250-3668. Details on the study design of these 2 studies can be found in Section II 2.7.3.2.3.2 of the full dossier assessment.

This deviates from the company's approach, which used the respective total population for the assessment of the added benefit of insulin degludec for all 4 studies.

Moreover, the company listed the NN1250-3643 extension study for the NN1250-3579 study in the table of the resulting study pool, but did not include it in its assessment. It was not clear from the available documents that the extension study was not relevant. On the contrary, the information provided in Module 4B suggests that a sufficient number of patients continued the study in the extension phase under randomized conditions.

Further information on the inclusion criteria for studies in this benefit assessment and on the information retrieval and the study pool derived from it can be found in Module 4B, Sections 4.2.2, 4.2.3 and 4.3.1.1 of the dossier, and in Sections II 2.7.3.2.1, II 2.7.3.2.3.1 and II 2.7.3.2.3.2 of the full dossier assessment.

II 2.4.1.1 Study characteristics

Table 5 and Table 6 describe the studies used for the assessment of research question B.

Table 5: Characteristics of the studies included – RCT, direct comparison: insulin degludec + OAD vs. human insulin/insulin analogues + metformin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NN1250-3579	RCT, phase 3, open-label, parallel, multicentre, treat-to-target	Adult patients with type 2 diabetes mellitus for ≥ 6 months, insulin-naive Pretreatment with metformin in monotherapy or in combination therapy with SUs, glinides, DPP-4 inhibitors, alpha-glucosidase inhibitors with unchanged dosing for at least 3 months HbA1c: 7.0–10.0%	IDeg + metformin ± DPP-4 inhibitors (N = 773)[c] IGlar + metformin ± DPP-4 inhibitors (N = 257)[c]	Treatment: 52 weeks Follow up: 1 week NPH insulin and OAD treatment NN1250-3643 extension study: 52 weeks	166 centres in Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Norway, Serbia, Spain, and United States 09/2009-01/2011	Primary outcome: change in HbA1c from baseline after 52 weeks Secondary outcomes: all-cause mortality, health-related quality of life, hypoglycaemias, adverse events
NN1250-3672	RCT, phase 3, open-label, parallel, multicentre, treat-to-target	Adult patients with type 2 diabetes mellitus for ≥ 6 months, insulin-naive[b] Pretreatment with metformin in monotherapy or in combination therapy with SUs, glinides, DPP-4 inhibitors, alpha-glucosidase inhibitors with unchanged dosing for at least 3 months HbA1c: 7.0–10.0%	IDeg + metformin ± DPP-4 inhibitors (N = 230)[c] IGlar + metformin ± DPP-4 inhibitors (N = 230)[c]	Treatment: 26 weeks Follow-up: 1 week, treatment with NPH insulin + OAD	106 centres in Canada, France, Ireland, Russia, South Africa, Ukraine, United Kingdom and United States 03/2010-11/2010	Primary outcome: change in HbA1c from baseline after 26 weeks Secondary outcomes: all-cause mortality, health-related quality of life, hypoglycaemias, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for the present benefit assessment.
b. Short-term administration of insulin (up to 14 days) and administration for more than 14 days were allowed, for example, in case of hospitalization.
c: At the time point of randomization, all ongoing OAD except metformin and DPP-4 inhibitors had to be discontinued. The proportion of the relevant subpopulation receiving only metformin as OAD was above 80% in each of the studies [3,4].

DPP-4: dipeptidyl peptidase 4; HbA1c: glycosylated haemoglobin; IDeg: insulin degludec; IGlar: insulin glargine; N: number of randomized patients; NPH: neutral protamine Hagedorn; OAD: oral antidiabetics; RCT: randomized controlled trials; SU: sulfonylurea; vs.: versus

Table 6: Characteristics of the interventions – RCT, direct comparison: insulin degludec + OAD vs. human insulin/insulin analogues + metformin

Study	Intervention	Comparison	Antidiabetic concomitant medication
NN1250-3579	IDeg 100 U/mL, subcutaneously, once daily with evening meal, insulin titration according to fixed algorithm[a]	IGlar 100 U/mL, subcutaneously, once daily at the same time[b], insulin titration according to fixed algorithm[a]	All OAD except metformin and DPP-4 inhibitors had to be discontinued at the time point of randomization.
NN1250-3672	IDeg 200 U/mL, subcutaneously, once daily with evening meal, insulin titration according to fixed algorithm[a]	IGlar 100 U/mL, subcutaneously, once daily at the same time[b], insulin titration according to fixed algorithm[a]	All OAD except metformin and DPP-4 inhibitors had to be discontinued at the time point of randomization.

a: The starting dose of insulin for IDeg and IGlar was 10 U. Dose adjustments according to the specifications for titration in the study protocol on the basis of the average of fasting plasma glucose (before breakfast, measured on 3 consecutive days) were conducted during the course of the study.
b: Time point according to (local) SPC.

DPP-4: dipeptidyl peptidase 4; IDeg: insulin degludec; IGlar: insulin glargine; OAD: oral antidiabetics; RCT: randomized controlled trials; SPC: Summary of Product Characteristics; U: units; vs.: versus

The studies NN1250-3579 and NN1250-3672 were randomized, open-label, multicentre approval studies with a treatment duration of 52 and 26 weeks. In the NN1250-3579 study, after the treatment phase (52 weeks), the patients could participate in an extension study (NN1250-3643) for another 52 weeks. All studies had a treat-to-target design, in which fasting plasma glucose was titrated to a specified goal.

Adult patients with type 2 diabetes mellitus who received metformin in monotherapy or in combination with various OAD (sulfonylureas, glinides, dipeptidyl peptidase 4 [DPP-4] inhibitors, alpha-glucosidase inhibitors) with unchanged dosing for at least 3 months were enrolled in the 2 studies. In both studies, all OAD except metformin and DPP-4 inhibitors had to be discontinued at the time point of randomization. In the NN1250-3579 study, 1030 patients were randomized in a ratio of 3:1 to treatment with insulin degludec (773 patients) or insulin glargine (257 patients), each in addition to metformin ± DPP-4 inhibitors. The NN1250-3672 study also investigated the comparison of insulin degludec with insulin glargine (each + metformin ± DPP-4 inhibitors). The 460 patients randomized were divided between the 2 studies in a ratio of 1:1 (230 patients per treatment arm).

The subpopulation of patients who were pretreated with metformin either in monotherapy or in combination therapy with an OAD except DPP-4 inhibitor and therefore received metformin as the sole OAD component during the course of the study was relevant for the present benefit assessment. The company presented no analyses limited to this subpopulation in Module 4B. According to information from publicly available documents, this requirement was fulfilled for over 80% of the study population, i.e. 1268 patients (82.5% in study NN1250-3579 [3] and 91.5% in study NN1250-3672 [4], Institute's calculation). Hence the

results of the total population of the studies NN1250-3579 and NN1250-3672 could have been used if the company had not objected to the use of information from Module 5.

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4B, Sections 4.3.1.2.1 and 4.3.1.2.2, and Appendix 4-E and 4-F of the dossier.

II 2.4.2 Results on added benefit

The company did not provide all complete necessary information for the assessment of the added benefit of insulin degludec + OAD in Modules 1 to 4. This includes, in Module 4B, data on confirmed hypoglycaemias (i.e. events in which both symptoms typical of hypoglycaemia occurred and a plasma glucose level of ≤ 70 mg/dL was determined) and for the individual components of the combined outcome "significant cardiovascular event". There was also no information on the results of the NN1250-3643 study, the extension study of the NN1250-3579 study.

The company objected to the use of data from Module 5, which is not to be published, for the present benefit assessment.

There were therefore no complete data for the research question on insulin degludec + OAD in type 2 diabetes mellitus. Hence the added benefit of insulin degludec + OAD versus the ACT specified by the G-BA is not proven. This deviates from the company's assessment, which claimed an indication of a considerable added benefit for this research question.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4B, Sections 4.2.5.2 and 4.3.1.3 of the dossier.

II 2.4.3 Extent and probability of added benefit

No proof of added benefit of insulin degludec + OAD for the treatment of type 2 diabetes mellitus in comparison with the ACT specified by the G-BA could be derived from the information presented by the company. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This deviates from the company's assessment, which claimed an indication of a considerable added benefit for this research question.

Further information on the extent and probability of the added benefit can be found in Module 4B, Section 4.4 of the dossier, and in Section II 2.7.3.2.8 of the full dossier assessment.

II 2.5 Research question C: insulin degludec + bolus insulin ± OAD

II 2.5.1 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 (Module 4C):

- study list on insulin degludec (studies completed up to 3 March 2014)
- bibliographical literature search on insulin degludec (last search on 17 February 2014)
- search in trial registries for studies on insulin degludec (last search on 19 February 2014)

To check the completeness of the study pool:

- bibliographical literature search on insulin degludec (last search on 16 May 2014)
- search in trial registries for studies on insulin degludec (last search on 10 June 2014)

The study identified from the steps of information retrieval mentioned that is relevant for the assessment of research question C is presented in Table 4.

Table 7: Study pool – RCT, direct comparison: insulin degludec + bolus insulin ± OAD vs. human insulin/insulin analogues ± metformin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
NN1250-3582[b] (with the NN1250-3667 extension study)	Yes	Yes	No

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
b: Over 80% of the patients included corresponded to the relevant subpopulation.
OAD: oral antidiabetics; RCT: randomized controlled trial; vs.: versus

The NN1250-3582 study (with the NN1250-3667 extension study) was identified for the research question of insulin degludec + bolus insulin ± OAD. Only a subpopulation was relevant for this study. However, no analyses for this relevant subpopulation were available in Module 4C of the dossier. In the NN1250-3582 study however, over 80% of the included patients corresponded to the relevant subpopulation. Hence it would have been possible to assess the added benefit of insulin degludec on the basis of the total populations, if the company had provided the complete necessary information on study methods and study results for publication (see Section II 2.5.2).

This approach deviates from that of the company, which assessed the added benefit of insulin degludec on the basis of the total population of the NN1250-3582 study.

Moreover, the company listed the NN1250-3667 extension study for the NN1250-3582 study in the table of the resulting study pool, but did not include it in its assessment. It was not clear from the available documents that the extension study was not relevant. On the contrary, the information provided in Module 4B suggests that a sufficient number of patients continued the study in the extension phase under randomized conditions.

Further information on the inclusion criteria for studies in this benefit assessment and on the information retrieval and the study pool derived from it can be found in Module 4C, Sections 4.2.2, 4.2.3 and 4.3.1.1 of the dossier, and in Sections II 2.7.4.2.1 and II 2.7.4.2.3 of the full dossier assessment.

II 2.5.1.1 Study characteristics

Table 8 and Table 9 describe the study used for the assessment of research question C.

Table 8: Characteristics of the studies included – RCT, direct comparison: insulin degludec + bolus insulin ± OAD vs. human insulin/insulin analogues ± metformin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NN1250-3582	RCT, phase 3, open-label, parallel, multicentre, treat-to-target	Adult patients with type 2 diabetes mellitus for ≥ 6 months Pretreatment with insulin ± OAD for at least 3 months HbA1c: 7.0–10%	IDeg + IAsp ± metformin ± pioglitazone (N = 755)[b] IGlar + IAsp ± metformin ± pioglitazone (N = 251)[b]	Treatment: 52 weeks Extension study (NN1250-3667): 26 weeks	123 centres in Bulgaria, Germany, Hong Kong, Ireland, Italy, Romania, Russia, Slovakia, South Africa, Spain, Turkey, United States 09/2009-10/2010	Primary outcomes: Change in HbA1c after 52 weeks of treatment Secondary outcomes: all-cause mortality, hypoglycaemias, health-related quality of life, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for the present benefit assessment.
b: At the time point of randomization, all ongoing OAD except metformin and pioglitazone had to be discontinued. The proportion of the relevant subpopulation receiving only metformin as OAD was above 80% in each of the studies.

HbA1c: glycosylated haemoglobin; IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; N: number of randomized patients; n: relevant subpopulation; OAD: oral antidiabetics; RCT: randomized controlled trial; vs.: versus

Table 9: Characteristics of the interventions – RCT, direct comparison: insulin degludec + bolus insulin ± OAD vs. human insulin/insulin analogues ± metformin

Study	Intervention	Comparison	Antidiabetic concomitant medication
NN1250-3582	Basal insulin IDeg 100 U/mL, subcutaneously, once daily with evening meal + bolus insulin IAsp subcutaneously with every meal insulin titration according to fixed algorithm[a]	Basal insulin IGlar 100 U/mL, subcutaneously once daily at the same time[b] + bolus insulin IAsp subcutaneously with every meal insulin titration according to fixed algorithm[a]	All OAD except metformin and pioglitazone had to be discontinued at the time point of randomization. Metformin and pioglitazone dosages were not to be changed during the treatment phase except for safety reasons.

a: The insulin starting dose (basal and bolus insulin) depended on the previous insulin regimen. Dose adjustments were conducted during the course of the study according to the specifications for titration in the study protocol on the basis of the average of fasting plasma glucose.
b: Time point according to local SPC.
IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; OAD: oral antidiabetics; RCT: randomized controlled trials; SPC: Summary of Product Characteristics; U: units; vs.: versus

The NN1250-3582 study was a randomized, open-label, multicentre approval study with a treatment duration of 52 weeks. After this treatment phase, the patients could participate in an extension study (NN1250-3667) for another 26 weeks. The study had a treat-to-target design, in which fasting plasma glucose was titrated to a specified goal.

Adult patients with type 2 diabetes mellitus who had received insulin treatment with or without OAD for at least 3 months were enrolled in the NN1250-3582 study. All OAD except metformin and pioglitazone had to be discontinued at the time point of randomization. The administration of these 2 antidiabetics (dose and frequency) was not to be changed during the treatment phase except for safety reasons.

In the NN1250-3582 study, a total of 1006 patients were randomized in a ratio of 3:1 to treatment with insulin degludec + insulin aspart ± metformin ± pioglitazone (755 patients) or with insulin glargine + insulin aspart ± metformin ± pioglitazone (251 patients).

The subpopulation of patients who were pretreated with metformin either in monotherapy or in combination therapy with an OAD except pioglitazone and therefore received metformin as the sole OAD component during the course of the study was relevant for the present benefit assessment. The company presented no analyses limited to this subpopulation in Module 4C. According to information from publicly available documents, this requirement was fulfilled for over 80% of the study population (approximately 93% in the insulin degludec group and approximately 95% in the insulin glargine group, Institute's calculation) [5]. Hence the results of the total population of the NN1250-3582 study could have been used if the company had not objected to the use of information from Module 5.

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4C, Sections 4.3.1.2.1 and 4.3.1.2.2, and Appendix 4-E and 4-F of the dossier.

II 2.5.2 Results on added benefit

The company did not provide all complete necessary information for the assessment of the added benefit of insulin degludec + bolus insulin ± OAD in Modules 1 to 4. This includes, in Module 4, data on confirmed hypoglycaemias (i.e. events in which both symptoms typical of hypoglycaemia occurred and a plasma glucose level of ≤ 70 mg/dL was determined). There was also no information on the results of the NN1250-3667 study, the extension study of the NN1250-3582 study.

The company objected to the use of data from Module 5, which is not to be published, for the present benefit assessment.

There were therefore no complete data for the research question on insulin degludec + bolus insulin ± OAD in type 2 diabetes mellitus. Hence the added benefit of insulin degludec + bolus insulin ± OAD versus the ACT specified by the G-BA is not proven.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4C, Sections 4.2.5.2 and 4.3.1.3 of the dossier.

II 2.5.3 Extent and probability of added benefit

No proof of added benefit of insulin degludec + bolus insulin ± OAD for the treatment of type 2 diabetes mellitus in comparison with the ACT specified by the G-BA could be derived from the information presented by the company. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This deviates from the company's assessment, which claimed an indication of a considerable added benefit for this research question.

Further information on the extent and probability of the added benefit can be found in Module 4C, Section 4.4 of the dossier, and in Section II 2.7.4.2.8 of the full dossier assessment.

II 2.6 Extent and probability of added benefit – summary

For the different subindications of insulin degludec for the treatment of type 2 diabetes mellitus, the resulting extent and probability of the added benefit compared with the relevant ACTs is shown in the overview in Table 10.

Table 10: Insulin degludec (type 2 diabetes mellitus): extent and probability of added benefit

Research question[a]	**Subindication**	**ACT**	**Extent and probability of added benefit**
A	Insulin degludec monotherapy	Human insulin	Added benefit not proven
B	Insulin degludec + OAD[b]	Human insulin + metformin (Note: If metformin is inappropriate according to the SPC, human insulin is to be used as treatment option.)	Added benefit not proven
C	Insulin degludec + bolus insulin ± OAD	Human insulin ± metformin[c]	Added benefit not proven

a: Designation corresponds to the coding in the company's dossier.
b: The G-BA's commission referred to the combination of insulin degludec with one or several other antidiabetics (except insulin). According to the approval status valid at the time point of the submission of the dossier, this subindication was limited to the combination of insulin degludec with OAD in analogy to the company's approach.
c: In combination with bolus insulin (without OAD) in the framework of intensified conventional insulin treatment, additional administration of metformin is not generally indicated.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetics; SPC: Summary of Product Characteristics

This assessment deviates from that of the company, which claimed an indication of considerable added benefit both for the subindication of insulin degludec + OAD (research question B) and for the subindication of insulin degludec + bolus insulin ± OAD (research question C) in type 2 diabetes mellitus.

The G-BA decides on the added benefit.

References for English extract

Please see full assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a14_13_insulin_degludec_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.6129.html.