IQWiG Reports – Commission No. A20-38

Insulin glargine/lixisenatide (type 2 diabetes mellitus) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Insulin glargin/Lixisenatid (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 July 2020). Please note: This document was translated by an external translator and 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] 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)
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)
SGLT	sodium-glucose linked transporter

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 fixed combination of insulin glargine and lixisenatide (insulin glargine/ lixisenatide). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 3 April 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of this report is to assess the added benefit of the fixed combination of insulin glargine and lixisenatide (insulin glargine/lixisenatide) as an adjunct to diet and exercise in addition to metformin and a sodium-glucose linked transporter (SGLT-2) inhibitor in comparison with the appropriate comparator therapy (ACT) in adults with insufficiently controlled type 2 diabetes mellitus.

In its specification of the ACT, the G-BA distinguished 2 patient groups. For the assessment, this results in 2 corresponding research questions, which are presented in Table 2.

Table 2: Research questions of the benefit assessment of insulin glargine/lixisenatide

Research question	Therapeutic indication	ACT[a]
A	Adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin)	▪ Human insulin + metformin or ▪ Human insulin + empagliflozin[b] or ▪ Human insulin + liraglutide[b] or ▪ Human insulin[c]
B	Adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug)	Optimization of the human insulin regimen (if applicable, + metformin or empagliflozin[b] or liraglutide[b])

a. Presentation of the respective ACT specified by the G-BA.
b. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further drugs for the treatment of cardiovascular risk factors, particularly antihypertensives, anticoagulants, and/or lipid-lowering drugs (regarding the operationalization, see the inclusion criteria of the EMPA-REG-Outcome study on empagliflozin and the LEADER study on liraglutide).
c. If the selected combination partners are contraindicated or not tolerated as per the SPCs or insufficiently effective due to advanced type 2 diabetes mellitus.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company departs from the ACT specified by the G-BA. Since the company neither identified any relevant study for its research questions nor excluded any relevant study

involving the ACT, the company's approach is of no consequence for the benefit assessment. For the present assessment, the ACT specified by the G-BA applies.

The assessment was conducted by means of patient-relevant outcomes on the basis of data presented by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of an added benefit.

Results

Research question A (Adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs [except insulin])

For research question A, no studies relevant for the benefit assessment were found. Hence, no data for assessing the added benefit of insulin glargine/lixisenatide in comparison with the ACT are available for adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin). This results in no hint of added benefit of insulin glargine/lixisenatide in comparison with the ACT. An added benefit is therefore not proven.

Research question B (adults with type 2 diabetes mellitus insufficiently controlled on insulin [with or without another blood glucose-lowering drug])

For research question B, no studies relevant for the benefit assessment were found. Hence, no data for assessing the added benefit of insulin glargine/lixisenatide in comparison with the ACT are available for adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug). This results in no hint of added benefit of insulin glargine/lixisenatide in comparison with the ACT. An added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Research question A (adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs [except insulin])

No data are available for assessing the added benefit of insulin glargine/lixisenatide in adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin). An added benefit of insulin glargine/lixisenatide is not proven for these patients.

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

Research question B (adults with type 2 diabetes mellitus insufficiently controlled on insulin [with or without another blood glucose-lowering drug])

No data are available for assessing the added benefit of insulin glargine/lixisenatide in adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug). An added benefit of insulin glargine/lixisenatide is not proven for these patients.

Summary

Table 3 presents a summary of the probability and extent of added benefit of insulin glargine/ lixisenatide.

Table 3: Insulin glargine/lixisenatide – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
A	Adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin)	▪ Human insulin + metformin or ▪ Human insulin + empagliflozin[b] or ▪ Human insulin + liraglutide[b] or ▪ Human insulin[c]	Added benefit not proven
B	Adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug)	Optimization of the human insulin regimen (if applicable, + metformin or empagliflozin[b] or liraglutide[b])	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further drugs for the treatment of cardiovascular risk factors, particularly antihypertensives, anticoagulants, and/or lipid-lowering drugs (regarding the operationalization, see the inclusion criteria of the EMPA-REG-Outcome study on empagliflozin and the LEADER study on liraglutide).
c. If the selected combination partners are contraindicated or not tolerated as per the SPCs or are insufficiently effective due to advanced type 2 diabetes mellitus.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of the fixed combination of insulin glargine and lixisenatide (hereinafter referred to as insulin glargine/lixisenatide) as an adjunct to diet and exercise in addition to metformin and a SGLT-2 inhibitor in comparison with the ACT in adults with insufficiently controlled type 2 diabetes mellitus.

In its specification of the ACT, the G-BA distinguished 2 patient groups. For the assessment, this results in 2 corresponding research questions, which are presented in Table 4.

Table 4: Research questions of the benefit assessment of insulin glargine/lixisenatide

Research question	Therapeutic indication	ACT[a]
A	Adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin)	▪ Human insulin + metformin or ▪ Human insulin + empagliflozin[b] or ▪ Human insulin + liraglutide[b] or ▪ Human insulin[c]
B	Adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug)	Optimization of the human insulin regimen (if applicable, + metformin or empagliflozin[b] or liraglutide[b])

a. Presentation of the respective ACT specified by the G-BA.
b. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further drugs for the treatment of cardiovascular risk factors, particularly antihypertensives, anticoagulants and/or lipid-lowering drugs (on the operationalization, see the inclusion criteria of the EMPA-REG-Outcome study on empagliflozin [3] and the LEADER study on liraglutide [4]).
c. If the selected combination partners are contraindicated or not tolerated as per the SPCs or are insufficiently effective due to advanced type 2 diabetes mellitus.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company departs from the ACTs specified by the G-BA. For both research questions, the company identifies the comparator therapy separately for the subpopulations with and without cardiovascular disease. The ACT chosen by the company is presented in Table 5.

Table 5: ACT specified by the company for the benefit assessment of insulin glargine/lixisenatide

Research question	Therapeutic indication		ACT specified by the company
A	Adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin)	Without cardiovascular disease	▪ Human insulin + empagliflozin or ▪ Human insulin[a]
		With cardiovascular disease	▪ Human insulin + empagliflozin or ▪ Human insulin + liraglutide or ▪ Human insulin[a]
B	Adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug)	Without cardiovascular disease	Optimization of the human insulin regimen[b] (ICT + empagliflozin)
		With cardiovascular disease	Optimization of the human insulin regimen[b] (ICT + empagliflozin) or optimization of the human insulin regimen[c] +liraglutide

a. If empagliflozin and liraglutide are contraindicated or not tolerated as per the SPCs or are insufficiently effective due to advanced type 2 diabetes mellitus.
b. Combination of long-acting basal insulin (longer-acting insulin, insulin glargine, insulin detemir) and short-acting bolus insulin (normal insulin, insulin glulisine, insulin aspart, insulin lispro).
c. Longer-acting insulin (NPH insulin) or a long-acting insulin analogue (insulin glargine, insulin detemir).

ACT: appropriate comparator therapy; ICT: intensified conventional therapy; NPH: neutral protamine Hagedorn

For adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin) (research question A), the company specifies human insulin in combination with empagliflozin as the ACT for patients without cardiovascular disease. For patients with cardiovascular disease, the company designates human insulin in combination with empagliflozin or in combination with liraglutide as the ACT. Where empagliflozin or liraglutide are contraindicated or not tolerated as per the SPC or are insufficiently effective due to advanced type 2 diabetes mellitus, the company designates human insulin as the ACT. This departs from the G-BA's specification of the ACT in that empagliflozin is specified as the ACT only for patients with manifest cardiovascular disease.

For adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug) (research question B), the company designates optimization of the human insulin regimen in combination with empagliflozin as the ACT in patients without cardiovascular disease. The company designates optimization of the human insulin regimen in combination with empagliflozin or with liraglutide as the ACT in patients with cardiovascular disease. Unlike the G-BA, the company restricts the optimization of human insulin to certain treatment regimen (see Table 5). This restriction is inappropriate. In accordance with the national disease management guideline [5], various forms of intensified insulin and combination therapies are generally available for this patient population. They include basal insulin supported oral therapy (BOT), supplementary insulin therapy (SIT) as well as conventional insulin therapy (CT) and intensified conventional insulin therapy (ICT), each also in combination with oral antidiabetic drugs. Furthermore, the company departs from the ACT in that the G-BA specifies empagliflozin as an ACT exclusively for patients with manifest cardiovascular disease.

The deviation from the ACT is not persuasive. For the present assessment, the ACT specified by the G-BA and presented in Table 4 applies.

Since the company neither identified any relevant study for its research questions nor excluded any relevant study involving the ACT (see Sections 2.3.1 and 2.4.1), the company's approach is of no consequence for the benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Research question A: Adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin)

2.3.1 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on insulin glargine/lixisenatide (status: 9 March 2020)
- Bibliographic literature search on insulin glargine/lixisenatide (most recent search on 9 March 2020)
- Search in trial registries / study results databases on insulin glargine/lixisenatide (most recent search on 19 March 2020)
- Search on the G-BA website on insulin glargine/lixisenatide (most recent search on 19 March 2020)

To check the completeness of the study pool:

- Search in trial registries on insulin glargine/lixisenatide (most recent search on 13 May 2020)

The company's dossier did not present any study on research question A. The check did not identify any relevant studies either.

2.3.2 Results on added benefit

The company does not present any data for assessing the added benefit of insulin glargine/lixisenatide in comparison with the ACT for adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin). This results in no hint of added benefit of insulin glargine/lixisenatide in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

The company does not present any data for assessing the added benefit of insulin glargine/lixisenatide in adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin). An added benefit of insulin glargine/ lixisenatide in comparison with the ACT is not proven for these patients.

This concurs with the company's assessment, which does not claim any added benefit for this patient group.

2.4 Research question B: Adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug)

2.4.1 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on insulin glargine/lixisenatide (status: 9 March 2020)

- Bibliographic literature search on insulin glargine/lixisenatide (most recent search on 9 March 2020)
- Search in trial registries / study results databases on insulin glargine/lixisenatide (most recent search on 19 March 2020)
- Search on the G-BA website on insulin glargine/lixisenatide (most recent search on 19 March 2020)

To check the completeness of the study pool:

- Search in trial registries on insulin glargine/lixisenatide (most recent search on 13 May 2020)

The company's dossier did not present any study on research question B. The check did not identify any relevant studies either.

2.4.2 Results on added benefit

The company does not present any data for assessing the added benefit of insulin glargine/ lixisenatide in comparison with the ACT for adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug). This results in no hint of added benefit of insulin glargine/lixisenatide in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The company does not present any data for assessing the added benefit of insulin glargine/lixisenatide in adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug). An added benefit of insulin glargine/ lixisenatide in comparison with the ACT is not proven for these patients.

This concurs with the company's assessment, which does not claim any added benefit for this patient group.

2.5 Probability and extent of added benefit – summary

Table 6 presents a summary of the result of the assessment of added benefit of insulin glargine/lixisenatide in comparison with the ACT.

Table 6: Insulin glargine/lixisenatide – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
A	Adults with type 2 diabetes mellitus insufficiently controlled on at least 2 blood glucose-lowering drugs (except insulin)	▪ Human insulin + metformin or ▪ Human insulin + empagliflozin[b] or ▪ Human insulin + liraglutide[b] or ▪ Human insulin[c]	Added benefit not proven
B	Adults with type 2 diabetes mellitus insufficiently controlled on insulin (with or without another blood glucose-lowering drug)	Optimization of the human insulin regimen (if applicable, + metformin or empagliflozin[b] or liraglutide[b])	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further drugs for the treatment of cardiovascular risk factors, particularly antihypertensives, anticoagulants, and/or lipid-lowering drugs (on the operationalization, see the inclusion criteria of the EMPA-REG-Outcome study on empagliflozin [3] and the LEADER study on liraglutide [4]).
c. If the selected combination partners are contraindicated or not tolerated as per the SPCs or are insufficiently effective due to advanced type 2 diabetes mellitus.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a20-38-insulin-glargine-lixisenatide-type-2-diabetes-mellitus-benefit-assessment-according-to-35a-social-code-book-v.13098.html.