IQWiG Reports – Commission No. A18-16

Insulin glargine/lixisenatide (type 2 diabetes mellitus) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Insulin glargin/Lixisenatid (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 May 2018). 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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-ratio combination of insulin glargine and lixisenatide (insulin glargine/ lixisenatide). 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 28 February 2018.

Research question

The aim of this report is to assess the added benefit of the fixed-ratio combination of insulin glargine and lixisenatide (insulin glargine/lixisenatide) in combination with metformin in the treatment of type 2 diabetes mellitus in adults to improve blood glucose control in the following approved indications:

- If metformin in combination with 1 other oral blood glucose-lowering drug insufficiently controls blood glucose levels,
- If metformin in combination with basal insulin insufficiently controls blood glucose levels.

Using the subindications provided by the G-BA, the assessment examined 2 research questions in comparison with the appropriate comparator therapies (ACTs) specified by the G-BA. The research questions are presented in Table 2.

Table 2[2]: Research questions for the benefit assessment of insulin glargine/lixisenatide in type 2 diabetes mellitus

Research question[a]	Indication	ACT[b]
1	Patients in whom metformin in combination with 1 other oral blood glucose-lowering drug insufficiently controls blood glucose levels[c]	Human insulin + metformin or Human insulin + empagliflozin[d] or Human insulin + liraglutide[d] or Human insulin[e]
2	Patients in whom metformin in combination with basal insulin insufficiently controls blood glucose levels[f]	Optimization of the human insulin regimen (possibly + metformin or empagliflozin[d] or liraglutide[d])

a: The approved indication "if metformin alone insufficiently controls blood glucose levels" has been disregarded as per specifications of the G-BA because in this treatment situation, insulin administration is typically not indicated, and this is therefore not a clinically relevant treatment situation.
b: Presentation of the respective ACT specified by the G-BA.
c: In the assessment referred to as: "Patients previously treated with 2 OADs".
d: Empagliflozin or liraglutide, each in combination with another drug for the treatment of cardiovascular risk factors, particularly antihypertensive drugs, anticoagulants and/or lipid-lowering drugs and only for patients with manifest cardiovascular disease (for operationalization, see study protocols of the respective outcome studies [3,4])
e: If the specified combination partners are incompatible or contraindicated according to the Summary of Product Characteristics or if they are insufficiently effective due to advanced type 2 diabetes mellitus
f: In the assessment referred to as: "Patients previously treated with insulin"
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral anti-diabetic drug

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Research question 1 (patients previously treated with 2 oral anti-diabetic drugs)

Study pool and study characteristics

The study pool for the benefit assessment of insulin glargine/lixisenatide in comparison with the ACT consists of the randomized controlled trial (RCT) LixiLan-O, in which insulin glargine/lixisenatide is compared with the insulin analogue insulin glargine (each in combination with metformin).

The 3-arm study included adult patients with type 2 diabetes mellitus in whom prior treatment with metformin alone or with metformin and 1 other OAD for at least 3 months failed to sufficiently control blood glucose levels. A total of 1170 patients were randomized to the 3 treatment arms insulin glargine/lixisenatide, insulin glargine, or lixisenatide (each in combination with metformin) in a 2:2:1 ratio. Concerning the 2 study arms which are relevant for this assessment, 469 patients were randomized to the insulin glargine/lixisenatide arm and 467 patients to the insulin-glargine arm. Patients previously treated with metformin and 1 other

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

OAD made up the assessment-relevant subpopulation of these treatment arms. This applies to 274 patients in the insulin glargine/lixisenatide arm and 270 patients in the insulin glargine arm.

The primary outcome of the study was the change in HbA1c from the start of the study to week 30. Health status and adverse events (AEs) were recorded as further patient-relevant outcomes.

Risk of bias

The risk of bias on the study level was rated low for the LixiLan-O study. For the outcomes all-cause mortality, cardiac and cerebral morbidity, SAEs, severe hypoglycaemia as well as renal function impairment, the risk of bias was also rated low. For the outcomes health state (EQ-5D VAS and Treatment Related Impact Measure for Diabetes [TRIM-D]), non-severe symptomatic hypoglycaemia and AEs (other specific AEs), the risk of bias was rated high.

Results

Mortality

- All-cause mortality

There were few deaths in either treatment arm. For the outcome all-cause mortality, no statistically significant difference was found between insulin glargine/lixisenatide + metformin and insulin glargine + metformin. Consequently, there is no hint of added benefit of insulin glargine/lixisenatide + metformin compared with insulin glargine + metformin; an added benefit is therefore not proven.

Morbidity

- Cardiac and cerebral morbidity

Few cardiac and cerebral events arose in the treatment arms. For the outcomes cardiac and cerebral morbidity, no statistically significant difference between the treatment arms was found. Consequently, there is no hint of added benefit of insulin glargine/lixisenatide + metformin compared with insulin glargine + metformin; an added benefit is therefore not proven.

- Health state (EQ-5D VASs, TRIM-D domains Daily Life and Psychological Health)

For the outcome health state (EQ-5D VAS and TRIM-D domains Daily Life and Psychological Health), no statistically significant difference between insulin glargine/lixisenatide + metformin and insulin glargine + metformin was found. Consequently, there is no hint of added benefit of insulin glargine/lixisenatide + metformin in comparison with insulin glargine + metformin. An added benefit is therefore not proven for this outcome.

Health-related quality of life

The LixiLan-O study did not collect any relevant data on health-related quality of life. Consequently, there is no hint of an added benefit of insulin glargine/lixisenatide + metformin

in comparison with insulin glargine + metformin for this outcome; an added benefit is therefore not proven.

Adverse events

- SAEs and discontinuation due to AEs

For the outcomes SAEs and discontinuation due to AEs, there is no statistically significant difference between treatment arms. Consequently, there is no hint of greater or lesser harm of insulin glargine/lixisenatide + metformin in comparison with insulin glargine + metformin; greater or lesser harm is therefore not proven.

- Symptomatic non-severe hypoglycaemia

For the outcome symptomatic non-severe hypoglycaemia, no statistically significant difference between treatment arms was found for plasma glucose values < 56 mg/dl or ≤ 70 mg/dl. Consequently, there is no hint of greater or lesser harm of insulin glargine/lixisenatide + metformin in comparison with insulin glargine + metformin; greater or lesser harm is therefore not proven.

- Severe hypoglycaemia

No severe hypoglycaemia occurred in either treatment group. Consequently, there is no hint of greater or lesser harm of insulin glargine/lixisenatide + metformin in comparison with insulin glargine + metformin; greater or lesser harm is therefore not proven.

- Renal impairment

Renal impairment occurred in one patient of each treatment arm. This results in no hint of greater or lesser harm of insulin glargine/lixisenatide + metformin in comparison with insulin glargine + metformin; greater or lesser harm is therefore not proven.

- Gastrointestinal disorders (including diarrhoea, nausea, vomiting)

For the specific AEs gastrointestinal disorders – including diarrhoea, nausea and vomiting – a statistically significant disadvantage of insulin glargine/lixisenatide + metformin in comparison with insulin glargine + metformin was found. This results in a hint of greater harm of insulin glargine/lixisenatide + metformin in comparison with insulin glargine + metformin.

Research question 2 (patients previously treated with insulin)

Study pool of the company

The company identified the open-label, multicentric, 3-arm RCT GetGoal-Duo 2. The study aimed to prove the efficacy, safety, and tolerability of a free combination of insulin glargine and lixisenatide (insulin glargine + lixisenatide) when compared to treatment with insulin glargine plus short-acting insulin glulisine. It included patients whose blood glucose levels were insufficiently controlled under prior treatment with basal insulin monotherapy or basal insulin in combination with 1 to 3 OADs, including metformin.

The study is not suitable for deriving conclusions on the added benefit of insulin glargine/ lixisenatide + metformin in comparison with the ACT specified by the G-BA. This is due to the following reasons:

- In the GetGoal-Duo 2 study, lixisenatide was administered as an add-on to the existing insulin glargine dose. This means that the dose ratios of insulin glargine and lixisenatide deviated from the fixed-ratio combination. Therefore, firstly, insulin glargine was overdosed during treatment initiation in the majority of patients according to the treatment specifications for the fixed-dose combination Secondly, the dose ratio of insulin glargine and lixisenatide at the start of the study and in the course of the study failed to match the ratio specified for the fixed-ratio combination.
- More than half of the patients required more than 60 units of insulin glargine already before randomization. However, the maximum daily dose of insulin glargine in the fixed-ratio combination is 60 units. For patients who already need more than 60 units of insulin, a dose beyond 60 units would be not be possible during treatment with the fixed-ratio combination. In addition, the Summary of Product Characteristics does not define a starting dose for these patients when switching to the fixed-ratio combination of insulin glargine/lixisenatide. Therefore, these patients do not qualify for treatment with the fixed-ratio combination.

Overall, there are no relevant data for assessing the added benefit of insulin glargine/lixisenatide for patients with prior insulin treatment.

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

On the basis of the results presented, the probability and extent of the added benefit of the fixed-ratio combination of insulin glargine and lixisenatide (insulin glargine/lixisenatide) compared with the ACT are assessed as follows:

Research question 1 (patients previously treated with 2 oral anti-diabetic drugs)

Overall, the data show exclusively negative effects (non-severe gastrointestinal events, considerable extent) for insulin glargine/lixisenatide + metformin in comparison with insulin glargine + metformin. In consideration of the noticeable difference, this results overall in a hint

[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].

of lower benefit of insulin glargine/lixisenatide + metformin in comparison with insulin glargine + metformin.

Due to the therapeutic focus on a uniform fasting plasma glucose value of 80 to 100 mg/dl, this is limited to patients with the treatment goal of maintaining near-normal blood glucose levels with basal-supported therapy. For patients without this treatment goal, an added benefit or lesser benefit is not proven.

Research question 2 (patients previously treated with insulin)

The company did not present any relevant data for the assessment of the added benefit of insulin glargine/lixisenatide in patients previously treated with insulin. An added benefit of insulin glargine/lixisenatide is therefore not proven for these patients.

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

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

Research question[a]	**Indication**	**ACT**[b]	**Probability and extent of added benefit**
1	Patients in whom metformin in combination with 1 other oral blood glucose-lowering drug insufficiently controls blood glucose levels[c]	Human insulin + metformin or Human insulin + empagliflozin[d] or Human insulin + liraglutide[d] or Human insulin[e]	*Therapeutic objective: Maintaining near-normal blood glucose levels:* Hint of lesser benefit *Other therapeutic objective:* Added benefit not proven
2	Patients in whom metformin in combination with basal insulin insufficiently controls blood glucose levels[f]	Optimization of the human insulin regimen (if applicable + metformin or empagliflozin[d] or liraglutide[d])	Added benefit not proven

a: The approved indication "if metformin alone insufficiently controls blood glucose levels" has been disregarded as per specifications of the G-BA because in this treatment situation, insulin administration is typically not indicated, and this is therefore not a clinically relevant treatment situation.
b: Presentation of the respective ACT specified by the G-BA.
c: In the assessment referred to as: "Patients previously treated with 2 OADs".
d: Empagliflozin or liraglutide, each in combination with another drug for the treatment of cardiovascular risk factors, particularly antihypertensive drugs, anticoagulants and/or lipid-lowering drugs and only for patients with manifest cardiovascular disease (for operationalization, see study protocols of the respective outcome studies [3,4])
e: If the specified combination partners are incompatible or contraindicated according to the Summary of Product Characteristics or if they are insufficiently effective due to advanced type 2 diabetes mellitus
f: In the assessment referred to as: "Patients previously treated with insulin"
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral anti-diabetic drug

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. 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/a18-16-insulin-glargine-lixisenatide-type-2-diabetes-mellitus-benefit-assessment-according-to-35a-social-code-book-v.8976.html.