IQWiG Reports – Commission No. A18-75

Semaglutide (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 *Semaglutid (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 January 2019). 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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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 semaglutide. 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 30 October 2018.

Research question

The purpose of this report is to assess the added benefit of semaglutide for the treatment of adults with type 2 diabetes mellitus for the following approved indications:

- **Monotherapy**: If diet and exercise alone fail to adequately control blood glucose in patients who are ineligible to use metformin due to intolerance or contraindications.
- **Add-on combination therapy**: In combination with other antihyperglycaemics, including insulin, if these drugs, combined with diet and exercise, fail to adequately control blood glucose.

The assessment is – following the G-BA's breakdown of therapeutic indications – conducted for 4 research questions by way of comparison with the G-BA's appropriate comparator therapy (ACT). These research questions are presented in Table 2.

Table 2[2]: Research questions of the benefit assessment for semaglutide

Research question	Indication[a]	ACT[b]
A	Monotherapy if diet and exercise alone fail to adequately control blood glucose in patients who are ineligible to use metformin due to intolerance or contraindications	▪ Sulfonylurea (glibenclamide or glimepiride)
B	Combination with another antihyperglycaemic (except for insulin) if this drug, combined with diet and exercise, fails to adequately control blood glucose	▪ **Metformin + sulfonylurea (glibenclamide or glimepiride)** or ▪ **Metformin + empagliflozin** or ▪ Metformin + liraglutide[c] or ▪ Human insulin if, according to the SPC, metformin is unsuitable due to intolerance or contraindication
C	Combination with at least 2 other antihyperglycaemics (excluding insulin) if these drugs, combined with diet and exercise, fail to adequately to control blood glucose	▪ **Human insulin + metformin** or ▪ Human insulin + empagliflozin[c] or ▪ Human insulin + liraglutide[c] or ▪ **Human insulin** if the combination partners defined as per the SPC are contraindicated or not tolerated or insufficiently effective due to advanced type 2 diabetes mellitus.
D	Combination with insulin, with or without another antihyperglycaemic if this drug, together with diet and exercise, fails to adequately control blood glucose	▪ **Optimization of the human insulin regimen** (if appropriate, + **metformin** or empagliflozin[c] or liraglutide[c])

a: Breakdown of the therapeutic indication according to the G-BA.
b: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
c: Empagliflozin or liraglutide, each in combination with other medications for the treatment of cardiovascular risk factors (particularly antihypertensives, anticoagulants, and/or lipid-lowering drugs) and only for patients with manifest cardiovascular disease (for operationalization, see the inclusion criteria of the relevant studies for empagliflozin [1] or liraglutide [2]).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The assessment was conducted by means of patient-relevant outcomes on the basis of randomized controlled trials (RCTs) with a minimum duration of 24 weeks.

Results

Research question A: Semaglutide monotherapy

The company identified no study for research question A. Consequently, there is no hint of added benefit of semaglutide monotherapy compared to the ACT. An added benefit is therefore not proven.

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

Research question B: Semaglutide plus another antihyperglycaemic drug excluding insulin

The company identified no study for research question B. Consequently, there is no hint of added benefit of semaglutide plus another antihyperglycaemic drug other than insulin compared with the ACT. An added benefit is therefore not proven.

Research question C: Semaglutide plus at least 2 other antihyperglycaemic drugs excluding insulin

The company identified no study for research question C. Consequently, there is no hint of added benefit of semaglutide plus at least 2 other antihyperglycaemic drugs excluding insulin compared with the ACT. An added benefit is therefore not proven.

Research question D: Semaglutide plus insulin (with or without another antihyperglycaemic drug)

The company identified no study for research question D. Consequently, there is no hint of added benefit of semaglutide plus insulin (with or without another antihyperglycaemic drug) compared with the ACT. An added benefit is therefore not proven.

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 added benefit of the drug semaglutide in comparison with the ACT is assessed as presented in Table 3:

[3] 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 [3,4].

Table 3: Semaglutide – probability and extent of added benefit

Research question	Indication	ACT[a]	Probability and extent of added benefit
A	Monotherapy if diet and exercise alone fail to adequately control blood glucose in patients who are ineligible to use metformin due to intolerance or contraindications	Sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Combination with another antihyperglycaemic (except for insulin) if this drug, combined with diet and exercise, fails to adequately control blood glucose	▪ **Metformin + sulfonylurea (glibenclamide or glimepiride)** or ▪ **Metformin + empagliflozin** or ▪ Metformin + liraglutide[b] or ▪ Human insulin if, according to the SPC, metformin is unsuitable due to intolerance or contraindication	Added benefit not proven
C	Combination with at least 2 other antihyperglycaemics (excluding insulin) if these drugs, combined with diet and exercise, fail to adequately to control blood glucose	▪ **Human insulin + metformin** or ▪ Human insulin + empagliflozin[b] or ▪ Human insulin + liraglutide[b] or ▪ **Human insulin** if the combination partners defined as per the SPC are contraindicated or not tolerated, or insufficiently effective due to advanced type 2 diabetes mellitus.	Added benefit not proven
D	Combination with insulin, with or without another antihyperglycaemic, if this drug, together with diet and exercise, fails to adequately control blood glucose	**Optimization of the human insulin regime** (if appropriate, + **metformin** or empagliflozin[b] or liraglutide[b])	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b: Empagliflozin or liraglutide, each in combination with other medications for the treatment of cardiovascular risk factors (particularly antihypertensives, anticoagulants, and/or lipid-lowering drugs) and only for patients with manifest cardiovascular disease (for operationalization, see the inclusion criteria of the relevant studies for empagliflozin [1] or liraglutide [2]).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

Additional outcome study – SUSTAIN 6 study – presented by the company

The company dossier describes the SUSTAIN 6 study for the following company-defined research question: Comparison of treatment with semaglutide in addition to standard treatment versus standard treatment (plus placebo) in patients at high cardiovascular risk. This research question corresponds to the design of the SUSTAIN 6 study.

Adult patients with type 2 diabetes mellitus and high cardiovascular risk are indicated for treatment with semaglutide and thus represent a subgroup under all 4 research questions mentioned above. For this subpopulation, an added benefit must be demonstrated versus the corresponding ACT as well. The company has not submitted such analyses. Given the design of the SUSTAIN 6 study, however, it is also questionable whether analyses relating to the research question for the SUSTAIN 6 study could be meaningfully interpreted.

Moreover, given the way it was conducted, the SUSTAIN 6 study was unsuitable for the intended comparison with "standard therapy". The results of the SUSTAIN 6 study show that antidiabetic therapy was completely inadequate in a large portion of patients, particularly for the following reasons:

- At the start of the study, the insulin dose in patients with an HbA1c value of ≤ 8.0% was to be lowered by 20% in all study arms and not be increased during the first 12 weeks. Therefore – despite the inclusion criteria of inadequate glycaemic control – these patients in the comparator arms were systematically undertreated during the first 12 weeks of the study.
- Antihyperglycaemic treatment was inadequate in a large percentage of patients. Adequate escalation of therapy – especially in the placebo arm – is not discernible even though patients were in need of escalation (mean HbA1c level at the beginning of the study: 8.7%). Despite being set forth in the study protocol, the existing escalation options were not exhausted.
- The high percentage of hypertensive patients whose systolic blood pressure was above the threshold of 140 mmHg over the course of the study suggests that the drug adjustment options for lowering systolic blood pressure had not been exhausted. However, there are no concrete analyses determining the percentage of patients with elevated systolic value who underwent escalation through dose increase or the use of an additional drug.

Therefore, the results of the study SUSTAIN 6 cannot be attributed to the drug semaglutide, but instead are potentially due to the inadequate treatment in the comparator arm.

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.

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373(22): 2117-2128.

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4. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-75-semaglutide-type-2-diabetes-mellitus-benefit-assessment-according-to-35a-social-code-book-v.10911.html.