IQWiG Reports – Commission No. A19-49

Empagliflozin/linagliptin (type 2 diabetes mellitus) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Empagliflozin/Linagliptin (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 August 2019). 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Empagliflozin/linagliptin (type 2 diabetes mellitus) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

29 May 2019

Internal Commission No.:

A19-49

Address of publisher:

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Keywords: empagliflozin, linagliptin, diabetes mellitus – type 2, benefit assessment

Table of contents

Page

List of tables ..... **iv**
List of abbreviations ..... **v**
2 Benefit assessment **1**
2.1 Executive summary of the benefit assessment **1**
2.2 Research question **3**
2.3 Information retrieval and study pool **3**
2.4 Results on added benefit **4**
2.5 Probability and extent of added benefit **4**
2.6 List of included studies **5**
References for English extract **6**

List of tables[2]

Page

Table 2: Research question of the benefit assessment of empagliflozin/linagliptin 1
Table 3: Empagliflozin/linagliptin – probability and extent of added benefit 2
Table 4: Research question of the benefit assessment of empagliflozin/linagliptin 3
Table 5: Empagliflozin/linagliptin – probability and extent of added benefit 5

[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)

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) with the benefit assessment of the fixed dose combination of empagliflozin and linagliptin (empagliflozin/linagliptin). 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 May 2019.

Research question

The aim of the present report is the assessment of the added benefit of the fixed dose combination of empagliflozin and linagliptin (empagliflozin/linagliptin) in comparison with the appropriate comparator therapy (ACT) for the treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control when metformin and/or sulphonylurea and one of the monocomponents of empagliflozin/linagliptin do not provide adequate glycaemic control.

Empagliflozin/linagliptin is additionally approved for adults already being treated with the free combination of empagliflozin and linagliptin. This subindication is not relevant for the benefit assessment, however, as linagliptin is currently not available in Germany.

The specification of the ACT by the G-BA resulted in the research question presented in Table 2 for the present benefit assessment.

Table 2: Research question of the benefit assessment of empagliflozin/linagliptin

Subindication	**ACT[a]**
Adults with type 2 diabetes mellitus with inadequate glycaemic control under treatment with at least 2 blood-glucose lowering drugs (except insulin, here metformin and/or sulphonylurea and empagliflozin or linagliptin) as an adjunct to diet and exercise[b]	▪ Human insulin + metformin or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ human insulin if, according to the SPC, the specified combination partners are not tolerated, contraindicated or not sufficiently effective due to advanced type 2 diabetes mellitus
a: Presentation of the ACT specified by the G-BA. b: Linagliptin is currently not available in Germany. Hence, pretreatment with linagliptin and metformin and/or sulphonylurea is not a relevant treatment situation for the German health care context. c: Empagliflozin or liraglutide, each in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for the operationalization, see study protocols of the respective outcome studies EMPA-REG OUTCOME [3] and LEADER [4]). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics	

The company concurred with the ACT specified by the G-BA. The present assessment was conducted in comparison with the ACT presented in Table 2.

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

Results

In its dossier, the company presented no data for the assessment of the added benefit of empagliflozin/linagliptin versus the ACT. This resulted in no hint of an added benefit of empagliflozin/linagliptin versus the ACT; an added benefit is therefore not proven.

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

Table 3 shows a summary of probability and extent of the added benefit of empagliflozin/ linagliptin.

Table 3: Empagliflozin/linagliptin – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Adults with type 2 diabetes mellitus with inadequate glycaemic control under treatment with at least 2 blood-glucose lowering drugs (except insulin, here metformin and/or sulphonylurea and empagliflozin or linagliptin) as an adjunct to diet and exercise[b]	▪ Human insulin + metformin or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ human insulin if, according to the SPC, the specified combination partners are not tolerated, contraindicated or not sufficiently effective due to advanced type 2 diabetes mellitus	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: Linagliptin is currently not available in Germany. Hence, pretreatment with linagliptin and metformin and/or sulphonylurea is not a relevant treatment situation for the German health care context. c: Empagliflozin or liraglutide, each in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for the operationalization, see study protocols of the respective outcome studies EMPA-REG OUTCOME [3] and LEADER [4]). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of the present report is the assessment of the added benefit of the fixed dose combination of empagliflozin and linagliptin (empagliflozin/linagliptin) in comparison with the ACT for the treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control when metformin and/or sulphonylurea and one of the monocomponents of empagliflozin/linagliptin do not provide adequate glycaemic control.

Empagliflozin/linagliptin is additionally approved for adults already being treated with the free combination of empagliflozin and linagliptin. This subindication is not relevant for the benefit assessment, however, as linagliptin is currently not available in Germany.

The specification of the ACT by the G-BA resulted in the research question presented in Table 4 for the present benefit assessment.

Table 4: Research question of the benefit assessment of empagliflozin/linagliptin

Subindication	**ACT[a]**
Adults with type 2 diabetes mellitus with inadequate glycaemic control under treatment with at least 2 blood-glucose lowering drugs (except insulin, here metformin and/or sulphonylurea and empagliflozin or linagliptin) as an adjunct to diet and exercise[b]	▪ Human insulin + metformin or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ human insulin if, according to the SPC, the specified combination partners are not tolerated, contraindicated or not sufficiently effective due to advanced type 2 diabetes mellitus
a: Presentation of the ACT specified by the G-BA. b: Linagliptin is currently not available in Germany. Hence, pretreatment with linagliptin and metformin and/or sulphonylurea is not a relevant treatment situation for the German health care context. c: Empagliflozin or liraglutide, each in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for the operationalization, see study protocols of the respective outcome studies EMPA-REG OUTCOME [3] and LEADER [4]). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics	

The company concurred with the ACT specified by the G-BA. The present assessment was conducted in comparison with the ACT presented in Table 4.

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 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 empagliflozin/linagliptin (status: 15 March 2019)
- bibliographical literature search on empagliflozin/linagliptin (last search on 15 March 2019)
- search in trial registries for studies on empagliflozin/linagliptin (last search on 15 March 2019)
- bibliographical literature search on the ACT (last search on 20 March 2019)
- search in trial registries for studies on the ACT (last search on 15 March 2019)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin/linagliptin (last search on 11 June 2019)

Concurring with the company, the check of the completeness of the study pool produced no RCTs that allow a direct comparison versus the ACT.

From its information retrieval for studies on an indirect comparison, the company identified the studies 1275.9 [5] and 1275.10 [6]. Study 1275.9 compared empagliflozin/linagliptin + metformin with linagliptin + metformin; and study 1275.10 compared empagliflozin/ linagliptin + metformin with empagliflozin + metformin. On the basis of these studies, the company searched for suitable RCTs with the ACT, in each case using the 2 common comparators linagliptin + metformin and empagliflozin + metformin, but did not identify any relevant studies. The Institute did not check the completeness of the study pool for the indirect comparison presented by the company.

2.4 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of empagliflozin/linagliptin versus the ACT. This resulted in no hint of an added benefit of empagliflozin/linagliptin versus the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The company presented no suitable data for the assessment of the added benefit of empagliflozin/linagliptin. An added benefit of empagliflozin/linagliptin versus the ACT is not proven for adults with type 2 diabetes mellitus with inadequate glycaemic control under treatment with at least 2 blood-glucose lowering drugs (except insulin, here metformin and/or sulphonylurea and empagliflozin or linagliptin) as an adjunct to diet and exercise.

The result of the assessment of the added benefit of empagliflozin/linagliptin in comparison with the ACT is summarized in Table 5.

Table 5: Empagliflozin/linagliptin – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adults with type 2 diabetes mellitus with inadequate glycaemic control under treatment with at least 2 blood-glucose lowering drugs (except insulin, here metformin and/or sulphonylurea and empagliflozin or linagliptin) as an adjunct to diet and exercise[b]	▪ Human insulin + metformin or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ human insulin if, according to the SPC, the specified combination partners are not tolerated, contraindicated or not sufficiently effective due to advanced type 2 diabetes mellitus	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: Linagliptin is currently not available in Germany. Hence, pretreatment with linagliptin and metformin and/or sulphonylurea is not a relevant treatment situation for the German health care context. c: Empagliflozin or liraglutide, each in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for the operationalization, see study protocols of the respective outcome studies EMPA-REG OUTCOME [3] and LEADER [4]). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit for empagliflozin/linagliptin.

The G-BA decides on the added benefit.

2.6 List of included studies

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

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. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. 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.

3. 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.

4. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375(4): 311-322.

5. Softeland E, Meier JJ, Vangen B, Toorawa R, Maldonado-Lutomirsky M, Broedl UC. Empagliflozin as add-on therapy in patients with type 2 diabetes inadequately controlled with linagliptin and metformin: a 24-week randomized, double-blind, parallel-group trial. Diabetes Care 2017; 40(2): 201-209.

6. Tinahones FJ, Gallwitz B, Nordaby M, Götz S, Maldonado-Lutomirsky M, Woerle HJ et al. Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: two 24-week randomized, double-blind, double-dummy, parallel-group trials. Diabetes Obes Metab 2017; 19(2): 266-274.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-49-empagliflozin-linagliptin-type-2-diabetes-mellitus-benefit-assessment-according-to-35a-social-code-book-v.12403.html.