IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-13

Empagliflozin/metformin – 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/Metformin – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 May 2016). 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/metformin – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
29 February 2016

Internal Commission No.:
A16-13

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Matthias Breidert, Hospitals in the Altmühltal Nature Park, Kösching, Germany

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.

IQWiG employees involved in the dossier assessment[2]:

- Gregor Moritz
- Wolfram Groß
- Ulrich Grouven
- Thomas Kaiser
- Anja Schwalm
- Ulrike Seay
- Siw Waffenschmidt

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

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

Table of contents

List of tables[3]

Page

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

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CSR	clinical study reports
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin
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)
SPC	Summary of Product Characteristics

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 drug combination empagliflozin/metformin. 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 February 2016.

Research question

The aim of this report was to assess the added benefit of the fixed combination of empagliflozin and metformin (hereinafter referred to as "empagliflozin/metformin") for the treatment of adults with type 2 diabetes mellitus in comparison with the appropriate comparator therapy (ACT) in the following approved subindications:

- **empagliflozin/metformin:** in patients inadequately controlled on their maximally tolerated dose of metformin alone
- **empagliflozin/metformin in combination with other blood-glucose lowering drugs, including insulin:** in patients inadequately controlled with metformin in combination with other blood-glucose lowering drugs, including insulin

Following the G-BA's subdivision of the therapeutic indication, the assessment was conducted for 3 research questions versus the ACT specified by the G-BA. These are shown in Table 2.

Table 2: Research questions of the benefit assessment of empagliflozin/metformin

Research question	Subindication[a]	ACT specified by the G-BA
A	Fixed combination of empagliflozin and metformin in patients inadequately controlled on their maximally tolerated dose of metformin alone as an adjunct to diet and exercise	Metformin plus sulfonylurea (glibenclamide, glimepiride)
B	Combination therapy with other blood-glucose lowering drugs except insulin in patients inadequately controlled with metformin in combination with these other blood-glucose lowering drugs, except insulin, as an adjunct to diet and exercise	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective)*
C	Combination therapy with insulin, with or without OAD, in patients inadequately controlled with metformin in combination with insulin as an adjunct to diet and exercise	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective)*
a: Subdivisions of the therapeutic indication according to the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic		

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: empagliflozin/metformin

For research question A, the company presented a study of direct comparison (1245.28) investigating empagliflozin/metformin in the 25 mg/day fixed dose (in combination with metformin). It additionally presented 3 further studies for 2 indirect comparisons to investigate empagliflozin in the 10 mg/day fixed dose (in combination with metformin). These 4 studies in total had already been presented in the first dossier and in the corresponding commenting procedure on empagliflozin (single agent).

Irrespective of the question whether the data presented by the company were at all relevant for the benefit assessment, the company's assessment was incomplete with regard to content because it did not analyse all relevant outcomes. Moreover, the documents presented by the company were self-contradictory.

Direct comparison

The company presented study 1245.28 to prove the added benefit of empagliflozin/metformin. It presented results from study 1245.28 at the data cut-offs 104 weeks and 208 weeks on a subpopulation of patients who had received a daily dose of at least 1700 mg metformin in the course of the treatment. This comprised about 70% of the total study population. Study 1245.28 cannot provide a sufficiently certain assessment of the blood-glucose lowering effect on the approval-compliant use of empagliflozin/metformin (starting dose 10 mg/day) in comparison with glimepiride/metformin (see first assessment A14-26).

In its analysis of the study 1245.28, the company did not present results on several patient-relevant outcomes, although it was already known from the first dossier assessment of empagliflozin, from the corresponding addendum and from the G-BA's decision which patient-relevant outcomes were relevant for the benefit assessment. In particular, the company partly did not analyse specific adverse events (AEs) in which a disadvantage of empagliflozin in comparison with glimepiride was shown (e.g. renal and urinary disorders).

Indirect comparisons

Since the company identified no study of direct comparison for the approval-compliant empagliflozin starting dose of 10 mg/day (plus metformin), it presented 2 indirect comparisons based on RCTs (referred to as "indirect comparisons I to IV"). The indirect comparison I (including the corresponding sensitivity analyses, referred to by the company as "indirect comparisons III and IV") was conducted with the common comparator empagliflozin 25 mg/day plus metformin, the indirect comparison II with the common comparator linagliptin + metformin. For all analyses, the company only considered the subpopulation of patients who had received a daily dose of at least 1700 mg metformin in the

course of the treatment. These were about 75% (study 1275.1), about 55% (study 1245.23/1245.31), and about 74% (study 1218.20) of the respective study population.

For its indirect comparison I, the company included the studies 1275.1 and 1245.23/1245.31 on the side of the intervention therapy, and the study 1245.28, which was already presented for the direct comparison, on the side of the comparator therapy. Hence this corresponds to the indirect comparison subsequently submitted in the commenting procedure on the first assessment; this indirect comparison could also only be interpreted to a limited extent because of the design of study 1245.28. As was the case for the direct comparison, analyses on relevant outcomes were missing, and there were contradictions in comparison with the information provided in the clinical study reports (CSRs) of the studies used. Due to the described deficiencies, the indirect comparison I presented by the company was also incomplete with regard to content. This also applied to the corresponding sensitivity analyses (referred to by the company as "indirect comparisons III and IV").

For its indirect comparison II, the company included study 1275.1 on the side of the intervention therapy, and study 1218.20 on the side of the comparator therapy. As described in the addendum to the first dossier assessment on empagliflozin (single agent), this indirect comparison was not usable for the benefit assessment because the studies were not sufficiently similar. In addition, no conclusive interpretation was possible for study 1218.20 (linagliptin + metformin versus glimepiride + metformin) because not drugs, but therapeutic strategies were compared in this study.

Summary

In summary, the company presented no data suitable for the benefit assessment. Hence the added benefit of empagliflozin/metformin is not proven.

Research question B: empagliflozin/metformin plus other blood-glucose lowering drugs except insulin

No relevant data were available for research question B. Hence the added benefit of empagliflozin/metformin plus other blood-glucose lowering drugs except insulin is not proven.

Research question C: empagliflozin/metformin plus insulin (with or without oral antidiabetic)

No relevant data were available for research question C. Hence the added benefit of empagliflozin/metformin plus insulin (with or without oral antidiabetic) is not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug combination empagliflozin/metformin compared with the ACT is assessed as presented in Table 3:

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

Research question	Subindication	ACT	Extent and probability of added benefit
A	Empagliflozin/metformin	Metformin plus sulfonylurea (glibenclamide, glimepiride)	Added benefit not proven
B	Empagliflozin/metformin plus other blood-glucose lowering drugs except insulin	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective)*	Added benefit not proven
C	Empagliflozin/metformin plus insulin (with or without OAD)	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective)*	Added benefit not proven
ACT: appropriate comparator therapy; OAD: oral antidiabetic			

The G-BA decides on the added benefit.

Research question additionally investigated by the company – study EMPA-REG-Outcome

In its dossier, the company described the study EMPA-REG-Outcome for the following research question defined by the company: comparison of treatment with empagliflozin/ metformin in addition to standard treatment versus standard treatment (plus placebo) in patients at high cardiovascular risk. This research question concurred with the design of the EMPA-REG-Outcome study. However, the company presented no analyses on the EMPA-REG-Outcome study that allow a comparison with the ACT. The company argued that a different comparator therapy (standard treatment) should be defined for patients at high cardiovascular risk, but its arguments were self-contradictory. A description of the study can be found in benefit assessment A16-12 on empagliflozin (single agent), which is published at the same time as the present benefit assessment of the fixed combination.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Irrespective of this, the EMPA-REG-Outcome study can be used for the research question whether additional administration of empagliflozin has an advantage in a situation in which the treating physicians do not exhaust the available treatment options except empagliflozin. However, this research question was not relevant for the present benefit assessment. In contrast, the EMPA-REG-Outcome study was unsuitable for the research question investigated by the company (comparison of empagliflozin plus standard treatment versus standard treatment [plus placebo] for the benefit assessment in Germany):

- On the one hand, the treatment used in the EMPA-REG-Outcome study was no adequate standard treatment. On the contrary, it was noted that neither the study definition of the necessity for escalation of the antihyperglycaemic therapy (according to the inclusion criteria, all patients had received inadequate treatment) nor the upper threshold values mentioned in the guidelines (more than 70% of the patients in the control group did not reach these threshold values) were consistently adhered to. In addition, by far the largest part of treatment escalation was not conducted during "regular" treatment, but as part of emergency treatment. The large proportion of hypertensive patients whose systolic blood pressure was above the threshold value of 140 mmHg over the course of the study suggests that the options of drug adjustment to lower systolic blood pressure were not exhausted. However, there were no specific analyses on the proportion of patients with increased systolic value whose treatment was escalated by dose increase or administration of a further drug.
- On the other hand, marked regional differences were shown in the results on patient-relevant outcomes. The difference observed in the total population in favour of empagliflozin was largely determined by a marked difference in the regions Latin America and Asia, whereas no such difference was shown in the region Europe. The company's dossier contained no analyses on the quality of treatment in the different regions.

2.2 Research question

The aim of this report was to assess the added benefit of the fixed combination of empagliflozin and metformin (hereinafter referred to as "empagliflozin/metformin") for the treatment of adults with type 2 diabetes mellitus in comparison with the ACT in the following approved subindications:

- **empagliflozin/metformin:** in patients inadequately controlled on their maximally tolerated dose of metformin alone
- **empagliflozin/metformin in combination with other blood-glucose lowering drugs, including insulin:** in patients inadequately controlled with metformin in combination with other blood-glucose lowering drugs, including insulin

Following the G-BA's subdivision of the therapeutic indication, the assessment was conducted for 3 research questions versus the ACT specified by the G-BA. These are shown in Table 4.

Table 4: Research questions of the benefit assessment of empagliflozin/metformin

Research question	Subindication[a]	ACT specified by the G-BA
A	Fixed combination of empagliflozin and metformin in patients inadequately controlled on their maximally tolerated dose of metformin alone as an adjunct to diet and exercise	Metformin plus sulfonylurea (glibenclamide, glimepiride)
B	Combination therapy with other blood-glucose lowering drugs except insulin in patients inadequately controlled with metformin in combination with these other blood-glucose lowering drugs, except insulin, as an adjunct to diet and exercise	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective)*
C	Combination therapy with insulin, with or without OAD, in patients inadequately controlled with metformin in combination with insulin as an adjunct to diet and exercise	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective)*
a: Subdivisions of the therapeutic indication according to the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic		

Regarding the ACT, the company followed the G-BA's specifications for all research questions.

The assessment was conducted based on patient-relevant outcomes and on 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.

Research question additionally investigated by the company

The company investigated an additional research question in its dossier: empagliflozin in addition to antidiabetic standard treatment in adult patients with type 2 diabetes mellitus and high cardiovascular risk in comparison with placebo treatment in addition to antidiabetic standard treatment. The company presented the study EMPA-REG-Outcome for this research question.

Adult patients with type 2 diabetes mellitus and high cardiovascular risk are a subpopulation of the approval population of empagliflozin and are therefore comprised by the 3 research questions mentioned above. The added benefit in comparison with the ACT has to be proven also for this subpopulation. The company did not present such an analysis. Irrespective of this, the study is described in Appendix A of benefit assessment A16-12 on empagliflozin (single agent) [3], which is published at the same time as the present benefit assessment of the fixed combination.

2.3 Research question A: empagliflozin/metformin

2.3.1 Information retrieval and study pool (research question A)

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 (status: 8 December 2015)
- bibliographical literature search on empagliflozin (last search on 10 December 2015)
- search in trial registries for studies on empagliflozin (last search on 18 December 2015)
- bibliographical literature search on the ACT (last search on 10 December 2015)
- search in trial registries for studies on the ACT (last search on 18 December 2015)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 18 March 2016)
- search in trial registries for studies on linagliptin (last search on 13 May 2016)

No studies other than the ones cited by the company in the dossier were identified from this check.

From the steps of information retrieval mentioned, the company identified one study of direct comparison (1245.28 [4]), and 4 studies for a total of 4 indirect comparisons (1245.28 [4], 1245.23/1245.31 [5], 1275.1 [6] and 1218.20 [7]). These 4 studies had already been presented in the first dossier and in the corresponding commenting procedure on empagliflozin (single agent) [8,9].

Irrespective of the question whether the data presented by the company were at all relevant for the benefit assessment, the company's assessment was incomplete with regard to content because it did not analyse all relevant outcomes. Moreover, the documents presented by the company were self-contradictory. This is further explained below.

Study of direct comparison 1245.28

The company presented study 1245.28 to prove the added benefit of empagliflozin. This was a randomized, active-controlled approval study sponsored by the company on the comparison of empagliflozin 25 mg/day versus glimepiride 1-4 mg/day, each in combination with metformin. The design and the study characteristics of study 1245.28 are described in detail in dossier assessment A14-26 [8].

As already explained extensively in the first assessment, study 1245.28 was not sufficiently interpretable for the benefit assessment [8]. This was caused, on the one hand, by the treatment regimen used in the control group (uniform blood-glucose lowering to the near-

normal level without individual target levels) in combination with the population included in the study (glycosylated haemoglobin [HbA1c] values partly already low at baseline). On the other hand, the starting dose of 25 mg/day empagliflozin used in the study was too high. According to the specifications in the Summary of Product Characteristics (SPC) [10,11], the recommended starting dose is exclusively 10 mg/day, however. Irrespective of this, no advantage of empagliflozin resulted from study 1245.28 overall because, compared with glimepiride, there were both positive and negative effects regarding AEs [8].

In Module 4 A, the company presented results from study 1245.28 at the data cut-offs 104 weeks and 208 weeks on a subpopulation of patients who had received a daily dose of at least 1700 mg metformin in the course of the treatment. This concurred with the requirements from the SPC for the fixed combination empagliflozin/metformin [12]. This subpopulation comprised about 70% of the total study population. However, results on several patient-relevant outcomes were not presented in Module 4 A. This was neither appropriate nor comprehensible because the company knew both from the first dossier assessment of empagliflozin and the corresponding addendum and from the G-BA's decision which patient-relevant outcomes were relevant for the benefit assessment [8,9,13]. In particular, the company partly did not analyse specific AEs in which a disadvantage of empagliflozin in comparison with glimepiride was shown (e.g. renal and urinary disorders). In addition, as in the first dossier, the company presented no adequate operationalization on the outcome "severe hypoglycaemias".

Indirect comparisons

Since the company identified no study of direct comparison for the approval-compliant empagliflozin starting dose of 10 mg/day, it presented 2 indirect comparisons based on RCTs (referred to as "indirect comparisons I to IV"). The indirect comparison I (including the corresponding sensitivity analyses, referred to by the company as "indirect comparisons III and IV") was conducted with the common comparator empagliflozin 25 mg/day plus metformin, the indirect comparison II with the common comparator linagliptin + metformin. Both indirect comparisons had already been presented in the first dossier and in the corresponding comment of the company on the dossier assessment [8,9]. For all analyses, the company only considered the subpopulation of patients who had received a daily dose of at least 1700 mg metformin during the course of the treatment, thus concurring with the requirements from the SPC for the fixed combination of empagliflozin/metformin [12]. The corresponding subpopulations were about 75% (study 1275.1), about 55% (study 1245.23/1245.31), and about 74% (study 1218.20) of the respective study population.

Indirect comparison I

The following Figure 1 shows the data referred to by the company as "indirect comparison I".

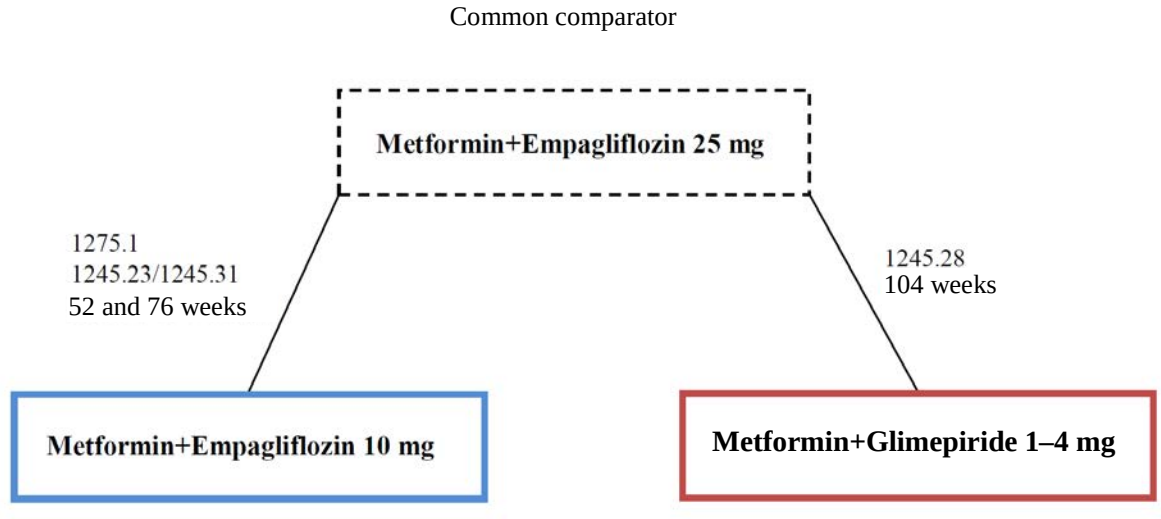

Figure 1: Data of the company for the indirect comparison I

The company included the studies 1275.1 and 1245.23/1245.31 on the side of the intervention therapy, and the study 1245.28, which was already presented for the direct comparison, on the side of the comparator therapy. Hence this comparison corresponds to the indirect comparison subsequently submitted in the commenting procedure on the first assessment; this indirect comparison could also only be interpreted to a limited extent because of the design of study 1245.28 (see above). At that time, the company presented only an analysis on the basis of 52 treatment weeks for all 3 studies, however. This was inadequate because the accompanying information loss was too large [9].

In Module 4 B of its dossier now submitted, the company presented analyses for 1 year (52 weeks; study 1275.1), 1.5 years (76 weeks, study 1245.23/31), and 2 years (104 weeks; study 1245.28). As was the case for the direct comparison, analyses on relevant outcomes were missing, however. In addition, for several outcomes, the data considered by the company for its analyses deviated from the information provided in the CSRs of the studies used. The company did not address the reasons for these deviations, however. Due to these contradictions, the effect estimates from the indirect comparison I presented by the company in Module 4 A were not usable.

Due to the described deficiencies, the indirect comparison I presented by the company was also incomplete with regard to content.

This also applied to the analyses referred to by the company as “indirect comparisons III and IV”. These analyses were sensitivity analyses on the indirect comparison I in which only one of both studies (1275.1 or 1245.23/31) was used for empagliflozin 10 mg/day.

Indirect comparison II

The following Figure 2 shows the data referred to by the company as "indirect comparison II".

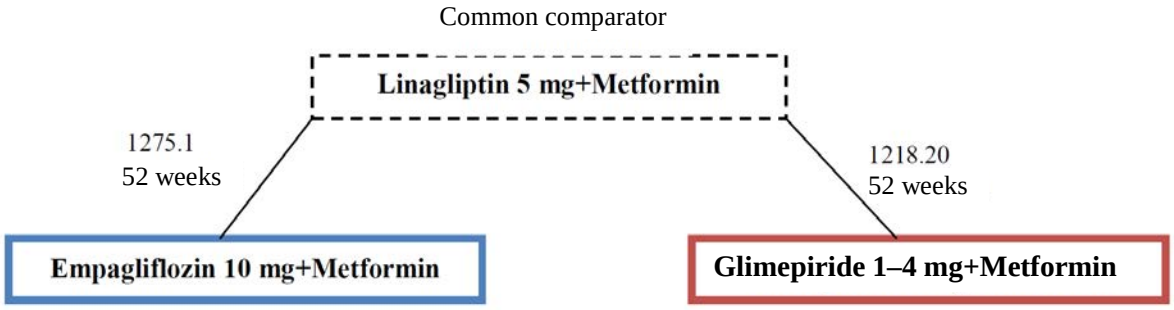

Figure 2: Data of the company for the indirect comparison II

Study 1275.1 was used on the side of the intervention therapy, and study 1218.20 on the side of the comparator therapy. As described in the first dossier assessment on empagliflozin, this indirect comparison was not usable for the benefit assessment because the studies were not sufficiently similar [9]. In addition, study 1218.20 was unsuitable for the benefit assessment also for the issues already discussed in the dossier assessment on linagliptin [14].

2.3.2 Results on added benefit (research question A)

The company presented no data suitable for the benefit assessment for research question A. Hence there was no hint of an added benefit of empagliflozin/metformin for adults with type 2 diabetes mellitus in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit (research question A)

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of empagliflozin/metformin.

This deviates from the company's assessment, which derived proof of a considerable added benefit for empagliflozin/metformin.

2.4 Research question B: empagliflozin/metformin plus other blood-glucose lowering drugs except insulin

2.4.1 Information retrieval and study pool (research question B)

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 (status: 8 December 2015)
- bibliographical literature search on empagliflozin (last search on 10 December 2015)

- search in trial registries for studies on empagliflozin (last search on 18 December 2015)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 18 March 2016)

No relevant studies were identified from this check. The company also identified no study for a comparison of empagliflozin/metformin plus other blood-glucose lowering drugs except insulin versus the ACT specified by the G-BA.

2.4.2 Results on added benefit (research question B)

The company presented no relevant data for research question B. Hence there was no hint of an added benefit of empagliflozin/metformin plus other blood-glucose lowering drugs except insulin in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit (research question B)

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of empagliflozin/metformin plus other blood-glucose lowering drugs except insulin. The company claimed no added benefit for this research question.

2.5 Research question C: empagliflozin/metformin plus insulin (with or without oral antidiabetic)

2.5.1 Information retrieval and study pool (research question C)

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 (status: 8 December 2015)
- bibliographical literature search on empagliflozin (last search on 10 December 2015)
- search in trial registries for studies on empagliflozin (last search on 18 December 2015)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 18 March 2016)

No relevant studies were identified from this check. The company also identified no studies suitable for assessing the added benefit of empagliflozin/metformin plus insulin (with or without oral antidiabetic) versus the ACT specified by the G-BA.

2.5.2 Results on added benefit (research question C)

The company presented no relevant data for research question C. Hence there was no hint of an added benefit of empagliflozin/metformin plus insulin (with or without oral antidiabetic)

for adults with type 2 diabetes mellitus in comparison with the ACT. An added benefit is therefore not proven.

2.5.3 Extent and probability of added benefit (research question C)

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of empagliflozin/metformin plus insulin (with or without oral antidiabetic). The company claimed no added benefit for this research question.

2.6 Extent and probability of added benefit – summary

An overview of the extent and probability of added benefit for the different subindications of empagliflozin in comparison with the relevant ACTs is given Table 5.

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

Research question	**Subindication**	**ACT**	**Extent and probability of added benefit**
A	Empagliflozin/metformin	Metformin plus sulfonylurea (glibenclamide, glimepiride)	Added benefit not proven
B	Empagliflozin/metformin plus other blood-glucose lowering drugs except insulin	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective)*	Added benefit not proven
C	Empagliflozin/metformin plus insulin (with or without OAD)	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective)*	Added benefit not proven
ACT: appropriate comparator therapy; OAD: oral antidiabetic			

For research question A (empagliflozin/metformin), this assessment deviates from that of the company, which claimed considerable added benefit for this research question. The company also claimed no added benefit for the subindications of research questions B and C.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 20.10.2015]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.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. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Empagliflozin: Nutzenbewertung gemäß § 35a SGB V; Auftrag A16-12. Köln: IQWiG; 2016.

4. Ridderstrale M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol 2014; 2(9): 691-700.

5. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2014; 37(6): 1650-1659.

6. DeFronzo RA, Lewin A, Patel S, Liu D, Kaste R, Woerle HJ et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care 2015; 38(3): 384-393.

7. Gallwitz B, Rosenstock J, Rauch T, Bhattacharya S, Patel S, Von Eynatten M et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet 2012; 380(9840): 475-483.

8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Empagliflozin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-26 [online]. 13.11.2014 [Accessed: 08.12.2014]. (IQWiG-Berichte; Volume 254). URL: https://www.iqwig.de/download/A14-26_Empagliflozin_Nutzenbewertung-35a-SGB-V.pdf.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Empagliflozin (Addendum zum Auftrag A14-26): Auftrag A14-50 [online]. 16.01.2015 [Accessed: 10.02.2015]. (IQWiG-Berichte; Volume 271). URL: https://www.iqwig.de/download/A14-50_Addendum-zum-Auftrag-A14-26_Empagliflozin.pdf.

10. Boehringer Ingelheim, Lilly. Jardiance 10 mg Filmtabletten: Fachinformation [online]. 11.2014 [Accessed: 15.04.2016]. URL: http://www.fachinfo.de/.

11. Boehringer Ingelheim. Jardiance 25 mg Filmtabletten: Fachinformation [online]. 12.2014 [Accessed: 15.04.2016]. URL: http://www.fachinfo.de/suche/fi/020249.

12. Boehringer Ingelheim, Lilly. Synjardy Filmtabletten: Fachinformation [online]. 22.10.2015 [Accessed: 15.04.2016]. URL: http://www.fachinfo.de/.

13. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage XII: Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Empagliflozin [online]. 05.02.2015 [Accessed: 06.04.2016]. URL: https://www.g-ba.de/downloads/39-261-2169/2015-02-05_AM-RL-XII_Empagliflozin_2014-08-15-D-123_BAnz.pdf.

14. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Linagliptin: erneute Nutzenbewertung gemäß § 35a Absatz 5b SGB V; Dossierbewertung; Auftrag A12-11 [online]. 29.11.2012 [Accessed: 11.03.2013]. (IQWiG-Berichte; Volume 144). URL: https://www.iqwig.de/download/A12-11_Linagliptin_Erneute_Nutzenbewertung_35a_Absatz_5b_SGB_V.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-13-empagliflozin/metformin-benefit-assessment-according-to-35a-social-code-book-v.7312.html.