

IQWiG Reports – Commission No. A14-07

Dapagliflozin/metformin – Benefit assessment according to §35a Social Code Book V¹

Extract

¹ Translation of Sections 2.1 to 2.6 of the dossier assessment *Dapagliflozin/Metformin – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 May 2014). 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:

Dapagliflozin/metformin – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

5 February 2014

Internal Commission No.:

A14-07

Address of publisher:

Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0

Fax: +49 (0)221 – 35685-1

E-Mail: berichte@iqwig.de

Internet: www.iqwig.de

Medical and scientific advice:

- Andreas Barthel, MVZ Endokrinologikum Ruhr, Bochum, 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 assessment²:

- Tatjana Kvitkina
- Andreas Gerber
- Thomas Kaiser
- Petra Kohlepp
- Ulrike Lampert
- Katrin Nink
- Sibylle Sturtz
- Min Zhou

Keywords: dapagliflozin, 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

	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	5
2.3 Research question A: dapagliflozin/metformin	7
2.3.1 Information retrieval and study pool	7
2.3.2 Research question A1: dapagliflozin/metformin versus sulfonylureas (glibenclamide, glimepiride) plus metformin.....	7
2.3.2.1 Results on added benefit	7
2.3.2.2 Extent and probability of added benefit.....	7
2.3.3 Research question A2: dapagliflozin/metformin versus glipizide plus metformin	8
2.3.3.1 Results on added benefit	9
2.3.3.2 Extent and probability of added benefit.....	9
2.3.4 List of included studies.....	9
2.4 Research question B: dapagliflozin/metformin plus insulin	10
2.4.1 Information retrieval and study pool	10
2.4.2 Results on added benefit.....	11
2.4.3 Extent and probability of added benefit	11
2.4.4 List of included studies.....	11
2.5 Research question C: dapagliflozin/metformin in combination with other blood-glucose lowering drugs except insulin	12
2.5.1 Information retrieval and study pool	12
2.5.2 Results on added benefit.....	12
2.5.3 Extent and probability of added benefit	12
2.5.4 List of included studies.....	12
2.6 Extent and probability of added benefit – summary	13
References for English extract	14

List of tables³

	Page
Table 2: Subindications and ACT for dapagliflozin/metformin	1
Table 3: Dapagliflozin/metformin – extent and probability of added benefit.....	4
Table 4: Subindications and ACT for dapagliflozin/metformin	5
Table 5: Dapagliflozin/metformin – extent and probability of added benefit.....	13

³ 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)
HbA1c	haemoglobin A1c
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 dapagliflozin/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 5 February 2014.

Research question

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

- **dapagliflozin/metformin:** in patients with inadequate glycaemic control on their maximum tolerated dose of metformin alone
- **dapagliflozin/metformin in combination with other blood-glucose-lowering drugs including insulin:** in patients with inadequate glycaemic control with metformin and these drugs

The assessment was conducted separately for 3 subindications versus the ACT specified by the G-BA.

Table 2: Subindications and ACT for dapagliflozin/metformin

Research question ^a	Subindication	ACT specified by the G-BA
A	Dapagliflozin/metformin	Sulfonylurea ^b (glimepiride or glibenclamide) plus metformin
B	Dapagliflozin/metformin plus insulin ^c	Human insulin plus metformin (Note: treatment only with human insulin if metformin is not sufficiently effective)
C	Dapagliflozin/metformin plus other blood-glucose lowering drugs except insulin	Human insulin plus metformin (Note: treatment only with human insulin if metformin is not sufficiently effective)

a: Designation corresponds to the coding in the company’s dossier.
b: The company cited metformin in combination with a sulfonylurea as ACT for this therapeutic indication, but without limitation to glibenclamide and glimepiride. According to the specifications by the G-BA, direct comparative studies versus glipizide were to be additionally assessed.
c: Including the combination with other blood-glucose lowering drugs possible according to the approval.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA specified sulfonylureas (glibenclamide, glimepiride) plus metformin as ACT for subindication A. According to the commission by the G-BA, direct comparative studies versus glipizide were additionally assessed. In this benefit assessment, the added benefit of dapagliflozin/metformin was therefore assessed versus the following comparator therapies:

- Research question A1: ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride] plus metformin)
- Research question A2: glipizide plus metformin

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: dapagliflozin/metformin

Research question A1: dapagliflozin/metformin versus sulfonylureas (glibenclamide, glimepiride) plus metformin

The company identified no comparative study on the assessment of dapagliflozin/metformin versus the ACT.

Research question A2: dapagliflozin/metformin versus glipizide plus metformin

The company used one direct comparative study (D1690C00004) versus glipizide plus metformin for research question A2. This was a randomized, active-controlled, double-blind approval study sponsored by the company, which the company already submitted for the dossier assessment of dapagliflozin (individual substance). As already described there, the D1690C00004 study is unsuitable for answering the research question of the benefit assessment. The analyses of this study additionally presented by the company for dapagliflozin/metformin did not change the assessment. The unsuitability is particularly due to the fact that, both in the intervention arm (dapagliflozin/metformin) and in the control arm (glipizide plus metformin), the treatments were not used in compliance with the approval status.

Dapagliflozin was up-titrated from 2.5 mg to 10 mg at 3-week intervals in the first 18 weeks, although the Summary of Product Characteristics (SPC) does not specify titration, but regular daily dosing of 10 mg. The sulfonylurea glipizide was also titrated in the study, which principally was in compliance with the approval, but the choice of titration steps was not. The titration step was 10 mg (from 10 mg to 20 mg) for patients who already received a dose of 10 mg, whereas the SPC only specifies steps of 2.5 mg or 5 mg. This considerable dose increase from 50% to 100% of the maximum dose can increase the risk of hypoglycaemia. Because both treatments were not administered in compliance with the approval, the effects observed in the study could not be interpreted for the approval-compliant use and therefore for the research question specified. Moreover, the patients did not receive their individual maximum tolerated dose of metformin; instead, the current metformin dose was even lowered

in some of the patients. In addition, the target blood glucose specified in the study is to be rated as very low (fasting plasma glucose < 110 mg/dL). According to current guidelines, lowering blood-glucose levels to near-normal levels should only be agreed on after individually balancing of benefits and risks and under consideration of individual factors.

Research question B: dapagliflozin/metformin plus insulin

The company included 3 randomized placebo-controlled studies (D1690C00006, D1690C00018 and D1690C00019) for research question B. The company also presented these studies for the assessment of the added benefit of dapagliflozin (individual substance). As already described there, these studies are unsuitable for assessing the added benefit because, in the comparator groups, it was largely prohibited to adapt the insulin therapy to individual requirements. Patients in both treatment arms in all 3 studies were required to continue their prior treatment with insulin unchanged, i.e. it was neither allowed to change the type of insulin nor the type of insulin therapy. The insulin dose could only be increased as an emergency medication in very high levels of fasting plasma glucose or HbA1c, and reduced in an increased risk of hypoglycaemia.

Because of the lack of opportunities for optimization – particularly in the respective comparator groups – and hence the lack of comparison versus the ACT, the 3 studies are unsuitable for drawing conclusions on the added benefit of dapagliflozin/metformin in combination with insulin. The analyses of these studies additionally presented by the company for dapagliflozin/metformin did not change the assessment.

Research question C: dapagliflozin/metformin in combination with other blood-glucose lowering drugs except insulin

The company identified no study on the assessment of dapagliflozin/metformin in combination with other blood-glucose lowering drugs except insulin versus the ACT.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

On the basis of the results presented, the extent and probability of the added benefit of the drug combination dapagliflozin/metformin compared with the ACT is assessed as follows:

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), see [1]. 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), see [2].

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

Research question	Subindication	ACT ^a	Extent and probability of added benefit
A1	Dapagliflozin/metformin	Sulfonylurea (glibenclamide, glimepiride) plus metformin	Added benefit not proven
A2	Dapagliflozin/metformin	Glipizide plus metformin ^b	Added benefit not proven
B	Dapagliflozin/metformin plus insulin ^c	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)	Added benefit not proven
C	Dapagliflozin/metformin plus other blood-glucose lowering drugs except insulin	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)	Added benefit not proven
<p>a: Presentation of the respective ACT specified by the G-BA unless marked otherwise. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.</p> <p>b: The company cited metformin in combination with a sulfonylurea as ACT for this therapeutic indication, but without limitation to glibenclamide and glimepiride. Glipizide was not specified as ACT by the G-BA, but according to the G-BA's specifications, direct comparative studies versus glipizide plus metformin were additionally assessed.</p> <p>c: Including the combination with other blood-glucose lowering drugs possible according to the approval.</p> <p>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics</p>			

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of dapagliflozin/metformin for the treatment of adult patients with type 2 diabetes mellitus in comparison with the ACT in the following approved subindications:

- **dapagliflozin/metformin:** in patients with inadequate glycaemic control on their maximum tolerated dose of metformin alone
- **dapagliflozin/metformin in combination with other blood-glucose-lowering drugs including insulin:** in patients with inadequate glycaemic control with metformin and these drugs

Following the company's research questions in the dossier, the assessment was conducted separately for 3 subindications versus the ACT specified by the G-BA. These are shown in Table 4.

Table 4: Subindications and ACT for dapagliflozin/metformin

Research question ^a	Subindication	ACT specified by the G-BA
A	Dapagliflozin/metformin	Sulfonylurea ^b (glimepiride or glibenclamide) plus metformin
B	Dapagliflozin/metformin plus insulin ^c	Human insulin plus metformin (Note: treatment only with human insulin if metformin is not sufficiently effective)
C	Dapagliflozin/metformin plus other blood-glucose lowering drugs except insulin	Human insulin plus metformin (Note: treatment only with human insulin if metformin is not sufficiently effective)

a: Designation corresponds to the coding in the company's dossier.
b: The company cited metformin in combination with a sulfonylurea as ACT for this therapeutic indication, but without limitation to glibenclamide and glimepiride. According to the specifications by the G-BA, direct comparative studies versus glipizide were to be additionally assessed.
c: Including the combination with other blood-glucose lowering drugs possible according to the approval.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

Research question A: dapagliflozin/metformin

The G-BA specified sulfonylureas (glibenclamide, glimepiride) plus metformin as ACT for this subindication. According to the specifications by the G-BA, direct comparative studies versus glipizide were to be additionally assessed. In this benefit assessment, the added benefit of dapagliflozin/metformin was therefore assessed versus the following comparator therapies:

- Research question A1: ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride] plus metformin)
- Research question A2: glipizide plus metformin

The company claimed to concur with the G-BA's specification on the ACT in principle. Nevertheless, in its research question it included studies with sulfonylureas without limitation to the drugs defined by the G-BA (see Section 2.7.2.1 of the full dossier assessment).

The valid SPC of glibenclamide or glimepiride was used for answering the question whether these drugs were administered according to their approval [3,4]. As glipizide is no longer approved in Germany, the SPC that was last valid in Germany was obtained from the Federal Institute for Drugs and Medical Devices (BfArM) and applied [5]. This was from the year 2000. The current SPC from Austria [6], where glipizide is still approved, was additionally used to also take into account the approval-compliant use of glipizide according to current knowledge.

Research question B: dapagliflozin/metformin plus insulin

The G-BA specified human insulin plus metformin (treatment only with human insulin if metformin is not sufficiently effective) as ACT for this subindication. The company stated to follow the ACT specified by the G-BA, but the dossier contained contradictory information on the implementation of the ACT (insulin instead of human insulin). The present assessment was conducted versus the ACT specified by the G-BA.

In the present assessment, research question B comprises the complete approval of the combination of dapagliflozin/metformin plus insulin, including a possible combination with other blood-glucose lowering drugs.

Research question C: dapagliflozin/metformin plus other blood-glucose lowering drugs except insulin

The G-BA specified human insulin plus metformin (treatment only with human insulin if metformin is not sufficiently effective) as ACT for this subindication. The company stated to follow the ACT specified by the G-BA, but the dossier contained contradictory information on the implementation of the ACT (insulin instead of human insulin). The present assessment was conducted versus the ACT specified by the G-BA.

Summary

In summary, the assessment of dapagliflozin/metformin in the different approved subindications was conducted versus the ACTs specified by the G-BA. For the research questions A (dapagliflozin/metformin), the added benefit versus glipizide plus metformin was also assessed. The assessment was conducted based on patient-relevant outcomes and on RCTs with a minimum duration of 24 weeks.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.2, 2.7.3 and 2.7.4 of the full dossier assessment.

2.3 Research question A: dapagliflozin/metformin

2.3.1 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 dapagliflozin/metformin (studies completed up to 20 November 2013)
- bibliographical literature search on dapagliflozin/metformin (last search on 27 January 2014)
- search in trial registries for studies on dapagliflozin/metformin (last search on 19 November 2013)

No relevant study was identified from the steps of information retrieval mentioned. Deviating from this, the company identified one study (D1690C00004), in which dapagliflozin plus metformin was compared with glipizide plus metformin. This study was unsuitable for assessing the added benefit of dapagliflozin/metformin versus glipizide plus metformin (research question A2). The reasons for exclusion of the D1690C00004 study are provided in Section 2.3.3 and in Section 2.7.2.4.2 of the full dossier assessment.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.2 and 2.7.2.4 of the full dossier assessment.

2.3.2 Research question A1: dapagliflozin/metformin versus sulfonyleureas (glibenclamide, glimepiride) plus metformin

The company did not submit any studies on the comparison of dapagliflozin/metformin versus the ACT specified by the G-BA (sulfonyleurea [glibenclamide or glimepiride] plus metformin). The only study the company included in the assessment was D1690C00004, which compared dapagliflozin/metformin with glipizide plus metformin (see Section 2.3.3).

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.3.2.1 Results on added benefit

No relevant data were available for research question A1. Hence the added benefit of dapagliflozin/metformin versus the ACT specified by the G-BA (sulfonyleurea [glibenclamide, glimepiride] plus metformin) is not proven.

2.3.2.2 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of dapagliflozin/metformin versus the ACT specified by the G-BA

(sulfonylurea [glibenclamide, glimepiride] plus metformin). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This assessment deviates from that of the company, which overall derived an indication of considerable added benefit versus sulfonylureas plus metformin without limitation to glibenclamide and glimepiride.

Further information about the extent and probability of the added benefit can be found in Module 4A, Section 4.4 of the dossier, and in Section 2.7.2.9 of the full dossier assessment.

2.3.3 Research question A2: dapagliflozin/metformin versus glipizide plus metformin

The company used one direct comparative study (D1690C00004) versus glipizide plus metformin. This was a randomized, active-controlled approval study sponsored by the company, which the company already submitted for the dossier assessment of dapagliflozin (individual substance) [7,8].

As already described in the assessment of dapagliflozin as individual substance, the D1690C00004 study is unsuitable for answering the research question of the benefit assessment. The analyses of this study additionally presented by the company for dapagliflozin/metformin did not change the assessment. The unsuitability is particularly due to the fact that, both in the intervention arm (dapagliflozin/metformin) and in the control arm (glipizide plus metformin), the treatments were not used in compliance with the approval status. Thus dapagliflozin was up-titrated from 2.5 mg to 10 mg at 3-week intervals in the first 18 weeks. Titration of the drug is not specified in the SPC, however, and the regular dosing of dapagliflozin is 10 mg daily [9]. The sulfonylurea glipizide was also titrated in the study, which principally was in compliance with the approval, but the choice of titration steps was not. The titration step was 10 mg (from 10 mg to 20 mg) for patients who already received a dose of 10 mg, whereas the SPC only specifies steps of 2.5 mg or 5 mg [6]. This considerable dose increase from 50% to 100% of the maximum dose can increase the risk of hypoglycaemia. Because both treatments were not administered in compliance with the approval, the effects observed in the study could not be interpreted for the approval-compliant use and therefore for the research question specified (see Section 2.7.2.4.2 of the full dossier assessment).

Moreover, the patients did not receive their individual maximum tolerated dose of metformin; instead, the current metformin dose was even lowered in some of the patients. In addition, the target blood glucose specified in the study is to be rated as very low (fasting plasma glucose < 110 mg/dL). According to current guidelines, lowering blood-glucose levels to near-normal levels should only be agreed on after individually balancing of benefits and risks and under consideration of individual factors [10].

More details on this can be found in Section 2.7.2.4.2 of the full dossier assessment as well as in the dossier assessment of dapagliflozin [7] and in the addendum to this assessment [8].

Overall, no relevant data were available for the assessment of the added benefit of dapagliflozin/metformin versus glipizide plus metformin.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.3.3.1 Results on added benefit

No relevant data were available for the research question A2 on dapagliflozin/metformin. Hence the added benefit of dapagliflozin/metformin versus glipizide plus metformin is not proven.

2.3.3.2 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of dapagliflozin/metformin versus glipizide plus metformin. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This assessment deviates from that of the company, which overall derived an indication of considerable added benefit versus sulfonylureas plus metformin.

Further information about the extent and probability of the added benefit can be found in Module 4A, Section 4.4 of the dossier, and in Section 2.7.2.9 of the full dossier assessment.

2.3.4 List of included studies

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of dapagliflozin/metformin versus the respective comparator therapy could be derived.

2.4 Research question B: dapagliflozin/metformin plus insulin

The research question comprises the complete approved therapeutic indication of the combination of dapagliflozin/metformin with insulin, including the possible combination with other blood-glucose lowering drugs.

2.4.1 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 dapagliflozin/metformin (studies completed up to 20 November 2013)
- bibliographical literature search on dapagliflozin/metformin (last search on 27 January 2014)
- search in trial registries for studies on dapagliflozin/metformin (last search on 19 November 2013)

The company presented 3 randomized placebo-controlled trials for the assessment of research question B on dapagliflozin/metformin plus insulin (D1690C00006, D1690C00018 and D1690C00019). The company also presented these studies for the assessment of the added benefit of dapagliflozin [7]. All 3 studies are unsuitable for assessing the added benefit versus the ACT (human insulin plus metformin) because, in the comparator groups, it was largely prohibited to adapt the insulin therapy to individual requirements. Thus patients in both treatment arms in all 3 studies were required to continue their prior treatment with insulin unchanged, i.e. it was neither allowed to change the type of insulin nor the type of insulin therapy. Only in the D1690C00006 study, it became possible to change regimen almost one year after enrolment of the first patient by amendment to the study protocol. However, this was only possible for the second half of the study (from week 25), and only if unexpected hypoglycaemia occurred and high levels of fasting plasma glucose or HbA1c at the same time. The insulin dose could only be increased as an emergency medication in very high levels of fasting plasma glucose or HbA1c, and reduced in an increased risk of hypoglycaemia (see Section 2.7.3.4.2 of the full dossier assessment).

Because of the lack of opportunities for optimization – particularly in the respective comparator groups – and hence the lack of comparison versus the ACT, the 3 studies are unsuitable for drawing conclusions on the added benefit of dapagliflozin/metformin in combination with insulin. The analyses of these studies additionally presented by the company for dapagliflozin/metformin did not change the assessment. See Section 2.7.3.4.2 of the full dossier assessment and the dossier assessment of dapagliflozin [7] for more information on the exclusion of the studies.

Overall, no relevant data were available for assessing the added benefit of dapagliflozin/metformin plus insulin versus human insulin plus metformin, neither for a direct comparison nor for an indirect comparison.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4 B, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.3.2 and 2.7.3.4 of the full dossier assessment.

2.4.2 Results on added benefit

No relevant data were available for research question B on dapagliflozin/metformin plus insulin. Hence the added benefit of dapagliflozin/metformin plus insulin versus human insulin plus metformin is not proven.

2.4.3 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of dapagliflozin/metformin plus insulin versus human insulin plus metformin. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This assessment deviates from that of the company, which overall derived an indication of minor added benefit versus metformin plus insulin.

Further information about the extent and probability of the added benefit can be found in Module 4A, Section 4.4 of the dossier, and in Section 2.7.3.9 of the full dossier assessment.

2.4.4 List of included studies

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of dapagliflozin/metformin plus insulin versus the ACT could be derived.

2.5 Research question C: dapagliflozin/metformin in combination with other blood-glucose lowering drugs except insulin

2.5.1 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 dapagliflozin/metformin (studies completed up to 20 November 2013)
- bibliographical literature search on dapagliflozin/metformin (last search on 27 January 2014)
- search in trial registries for studies on dapagliflozin/metformin (last search on 19 November 2013)

The company did not identify any relevant study from the steps of information retrieval mentioned.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier.

2.5.2 Results on added benefit

No relevant data were available for research question C on dapagliflozin/metformin in combination with other blood-glucose lowering drugs except insulin. Hence the added benefit of dapagliflozin/metformin in combination with other blood-glucose lowering drugs except insulin versus human insulin plus metformin is not proven.

2.5.3 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of dapagliflozin/metformin in combination with other blood-glucose lowering drugs except insulin versus human insulin plus metformin. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This concurs with the company's result.

Further information on the extent and probability of the added benefit can be found in Module 4A, Section 4.4 of the dossier.

2.5.4 List of included studies

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of dapagliflozin/metformin in combination with other blood-glucose lowering drugs except insulin versus the ACT could be derived.

2.6 Extent and probability of added benefit – summary

An overview of the extent and probability of added benefit for the different subindications of dapagliflozin/metformin in comparison with the respective ACT or versus glipizide plus metformin is given below:

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

Research question	Subindication	ACT ^a	Extent and probability of added benefit
A1	Dapagliflozin/metformin	Sulfonylurea (glibenclamide, glimepiride) plus metformin	Added benefit not proven
A2	Dapagliflozin/metformin	Glipizide plus metformin ^b	Added benefit not proven
B	Dapagliflozin/metformin plus insulin ^c	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)	Added benefit not proven
C	Dapagliflozin/metformin plus other blood-glucose lowering drugs except insulin	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA unless marked otherwise. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.

b: The company cited metformin in combination with a sulfonylurea as ACT for this therapeutic indication, but without limitation to glibenclamide and glimepiride. Glipizide was not specified as ACT by the G-BA, but according to the G-BA's specifications, direct comparative studies versus glipizide plus metformin were additionally assessed.

c: Including the combination with other blood-glucose lowering drugs possible according to the approval.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

This assessment deviates from that of the company, which overall derived an indication of considerable added benefit versus sulfonylureas plus metformin for research question A. For research question B, the company derived an indication of minor added benefit versus metformin plus insulin.

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 4.1 [online]. 28 November 2013 [accessed: 7 February 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.
2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.
3. TEVA. Glimepirid-TEVA 1mg/- 2 mg/- 3 mg/- 4 mg Tabletten: Fachinformation [online]. November 2013 [accessed: 19 March 2014]. URL: <http://www.fachinfo.de>.
4. AbZ-Pharma. Gliben-CT 1,75 mg Tabletten, Gliben-CT 3,5 mg Tabletten: Fachinformation [online]. August 2013 [accessed: 19 March 2014]. URL: <http://www.fachinfo.de>.
5. Pfizer. Glibenese: Fachinformation [unpublished]. 2000.
6. Pfizer. Minidiab 5mg Tabletten: Fachinformation [unpublished]. 2013.
7. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dapagliflozin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A12-18 [online]. 12 March 2013 [accessed: 18 March 2013]. (IQWiG-Berichte; Volume 155). URL: https://www.iqwig.de/download/A12-18_Dapagliflozin_Nutzenbewertung_35a-SGB-V.pdf.
8. Institute for Quality and Efficiency in Health Care. Addendum to commission A12-18 (dapagliflozin): commission A13-18 [online]. 29 April 2013 [accessed: 20 February 2014]. URL: https://www.iqwig.de/download/A13-18_Addendum-to-Commission-A12-18_Dapagliflozin.pdf.
9. Astra Zeneca, Bristol-Myers Squibb. Xigduo 5 mg/850 mg Filmtabletten, Xigduo 5 mg/1000 mg Filmtabletten: Fachinformation [online]. January 2014 [accessed: 6 February 2014]. URL: <http://www.fachinfo.de>.
10. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes: Langfassung; Version 2 [online]. September 2013 [accessed: 18 February 2014]. URL: http://www.versorgungsleitlinien.de/themen/diabetes2/dm2_therapie/pdf/NVL-DM2-Ther-lang-2.pdf.

The full report (German version) is published under

https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a14_07_dapagliflozin/metformin_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.6010.html