IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A14-27

Canagliflozin/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 *Canagliflozin/Metformin – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 November 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:
Canagliflozin/metformin – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
15 August 2014

Internal Commission No.:
A14-27

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
DPP	dipeptidyl peptidase
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP	glucagon-like peptide
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
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 canagliflozin/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 15 August 2014.

Research question

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

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

The assessment was conducted separately for 3 research questions versus the appropriate comparator therapy (ACT). The G-BA specified the ACT presented in Table 2.

Table 2: Subindications, research questions and ACT on canagliflozin/metformin considered in the benefit assessment

Subindication[a]	**Research question of the company**[b]	**ACT specified by the G-BA**
Canagliflozin/metformin	A Canagliflozin/metformin	Sulfonylurea (glibenclamide or glimepiride) plus metformin
Canagliflozin/metformin in combination with other blood-glucose lowering drugs, including insulin	B Canagliflozin/metformin plus sulfonylurea C Canagliflozin/metformin plus insulin	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)
a: Subdivisions of the therapeutic indication according to the G-BA. b: Designation corresponds to the coding in the company's dossier. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The research questions presented by the company do not cover the entire approved therapeutic indication of canagliflozin/metformin. The company noted in the dossier that further

combination therapies are approved, but, referring to the lack of clinical data, did not submit any corresponding modules. An added benefit for these combination therapies is not proven.

Results

Research question A: canagliflozin/metformin

The company specified glimepiride plus metformin as comparator therapy in research question A, and thus followed the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride] plus metformin). However, it also defined a specific patient population for which treatment with sulfonylureas is approved according to the Summary of Product Characteristics (SPC), but not applicable from the company's point of view. The company named sitagliptin plus metformin as alternative comparator therapy for this patient population. In the present benefit assessment, the specific patient population named by the company is considered to be an irrelevant subpopulation in the therapeutic indication and is not considered further.

Comparison versus the ACT: canagliflozin plus metformin versus glimepiride plus metformin

The company presented the randomized 3-arm approval study DIA3009 sponsored by the company for the comparison versus the ACT. This study compared canagliflozin plus metformin with glimepiride plus metformin with all patients continuing their prior metformin therapy at a stable dose as concomitant treatment. Whereas the daily dose of canagliflozin was 100 mg and 300 mg and was not changed, glimepiride was to be titrated. After a starting dose of 1 mg/day, dose steps of 2, 4, and 6 mg/day and – if approved in the respective country – 8 mg/day were envisaged (dose levels 1 to 5) for titration in the glimepiride arm. To maintain blinding, the randomized study medication was also made available in the levels 1 to 5 for sham titration in both canagliflozin arms. Each level corresponded to 100 mg/day or 300 mg/day of canagliflozin. The dose level was to be increased if at least 50% of fasting plasma glucose measurements were above a target value of 110 mg/dL during the 2 weeks preceding the study visit/titration (at least 3 measurements were recommended). The interval between 2 dose level increases could be reduced to less than one week if a patient had higher blood glucose levels and the conditions for increasing the dose level were fulfilled. The dose level was not to be increased if, during the 2 weeks preceding the study visit, hypoglycaemias had occurred that, from the investigator's point of view, excluded an increase of the dose level.

Hence in the DIA3009 study, there were relevant differences between the treatment arms with regard to the specified target blood glucose levels and the therapeutic strategies determined by them. In the canagliflozin arms of the study, target blood glucose levels could not be aimed at by dose adaptation ("titration" to target levels was performed without dose changes and merely to maintain blinding) and fixed dosage was used. In the glimepiride arm, in contrast, titration was specified by an algorithm and orientated towards near-normal target levels. The substantial differences in blood-glucose lowering between the treatment groups in the first weeks of the study were apparently induced by the one-sided possibility of reaching target levels for glimepiride. The time course of the occurrence of the key outcomes of the DIA3009

study (hypoglycaemias) corresponded to the course of blood glucose lowering. The results of the DIA3009 study could not be used for assessing the added benefit of canagliflozin plus metformin versus the ACT specified by the G-BA because it remained unclear whether the observed effects are attributable to the drugs or to the therapeutic strategy.

Further points in the DIA3009 study (e.g. use of canagliflozin in a starting dose of 100 mg/day without the possibility of dose increase or the use of a starting dose of 300 mg/day) are not discussed because they were not primarily relevant for the exclusion of the study.

Research question B: canagliflozin/metformin plus sulfonylurea

In research question B, the G-BA specified human insulin plus metformin as ACT with the note that only human insulin is to be used as treatment option if metformin is not sufficiently effective.

The company claimed no added benefit because the studies DIA3002 and DIA3010 it presented allowed no direct comparison of canagliflozin/metformin plus sulfonylureas versus human insulin plus metformin. For the indirect comparison, the literature search conducted by the company resulted in no relevant studies with the necessary common comparator.

Research question C: canagliflozin/metformin plus insulin

The company identified no comparative study for the assessment of canagliflozin/metformin plus insulin versus the ACT for research question C and claimed no added benefit.

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 canagliflozin/metformin compared with the ACT is assessed as presented in Table 3.

[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: Canagliflozin/metformin – extent and probability of added benefit

Research question[a]	**Subindication**	**ACT**	**Extent and probability of added benefit**
A	Canagliflozin/metformin	Sulfonylurea (glibenclamide or glimepiride) plus metformin	Added benefit not proven
B	Canagliflozin/metformin plus sulfonylurea	Human insulin plus metformin or only human insulin if metformin is not sufficiently effective	Added benefit not proven
C	Canagliflozin/metformin plus insulin	Human insulin plus metformin or only human insulin if metformin is not sufficiently effective	Added benefit not proven
a: Designation corresponds to the coding in the company's dossier. b: The comparator therapy chosen by the company is printed in **bold**. ACT: appropriate comparator therapy			

The research questions presented by the company do not cover the entire approved therapeutic indication of canagliflozin/metformin. The company noted in the dossier that further combination therapies are approved, but, referring to the lack of clinical data, did not submit any corresponding modules. An added benefit for these combination therapies is not proven.

The G-BA decides on the added benefit.

2.2 Research questions

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

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

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

Table 4: Subindications, research questions and ACT on canagliflozin/metformin considered in the benefit assessment

Subindication[a]	**Research question of the company**[b]	**ACT specified by the G-BA**
Canagliflozin/metformin	A Canagliflozin/metformin	Sulfonylurea (glibenclamide or glimepiride) plus metformin
Canagliflozin/metformin in combination with other blood-glucose lowering drugs, including insulin.	B Canagliflozin/metformin plus sulfonylurea C Canagliflozin/metformin plus insulin	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)
a: Subdivisions of the therapeutic indication according to the G-BA. b: Designation corresponds to the coding in the company's dossier. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The research questions considered by the company do not cover the entire approved therapeutic indication of canagliflozin/metformin. The company itself noted in the dossier that further combination therapies are approved, e.g. combinations of canagliflozin/metformin with dipeptidyl peptidase (DPP) 4 inhibitors, glinides, glucagon-like peptide (GLP) 1 receptor antagonists and α-glucosidase inhibitors. According to the company, there are no clinical data to investigate an added benefit of canagliflozin/metformin in the combinations mentioned. The company therefore submitted no modules on these combinations.

Research question A: canagliflozin/metformin

The benefit assessment for canagliflozin/metformin was conducted in comparison with the ACT (sulfonylurea [glibenclamide, glimepiride] plus metformin) specified by the G-BA. The company followed this specification and chose glimepiride plus metformin as ACT.

However, the company additionally defined a specific patient population for which, from the company's point of view, treatment with sulfonylureas is not applicable. The company named sitagliptin plus metformin as ACT for this population. For the present benefit assessment, the patients who cannot be treated with sulfonylureas are considered to be a subpopulation in the therapeutic indication, which cannot be clearly defined. The patient population was therefore not considered.

Research question B: canagliflozin/metformin plus sulfonylurea

The benefit assessment of canagliflozin/metformin plus sulfonylurea was conducted versus the ACT specified by the G-BA (human insulin plus metformin with the note that only human insulin is to be used if metformin is not sufficiently effective according to the SPC). The company followed this specification without considering the specific note by the G-BA. In the definition of the research question, the company added that it included additional studies with insulin analogues in its assessment.

Research question C: canagliflozin/metformin plus insulin

The benefit assessment of canagliflozin/metformin plus insulin was conducted versus the ACT specified by the G-BA (human insulin plus metformin with the note that only human insulin is to be used if metformin is not sufficiently effective according to the SPC). The company concurred with this specification.

Summary

In summary, the assessment of canagliflozin/metformin in the different approved subindications was conducted versus the ACTs specified by the G-BA. The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials with a minimum duration of 24 weeks.

Further information about the research question can be found in Modules 3A to 3C, Sections 3.1, and in Modules 4A to 4C, Sections 4.2.1, of the dossier, and in Sections 2.7.1, 2.7.2, 2.7.3 and 2.7.4 of the full dossier assessment.

2.3 Research question A: canagliflozin/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 lists on canagliflozin/metformin (studies completed up to 19 May 2014)
- bibliographical literature search on canagliflozin (last search on 16 May 2014)
- search in trial registries for studies on canagliflozin (last search on 21 May 2014)

From the steps of information retrieval mentioned, the company identified 2 studies (DIA3009 and DIA3006) in which canagliflozin/metformin was compared with glimepiride/metformin or sitagliptin/metformin. These studies were unsuitable for the assessment of the added benefit of canagliflozin/metformin in comparison with the ACT specified by the G-BA.

Reasons for exclusion of the studies DIA3009 and DIA3006

Study DIA3009

The company presented the randomized 3-arm approval study DIA3009 sponsored by the company for the comparison versus the ACT. This study compared canagliflozin plus metformin (free combination) with glimepiride plus metformin with all patients continuing their prior metformin therapy at a stable dose as concomitant treatment. Whereas the daily dose of canagliflozin was 100 mg or 300 mg and was not changed, glimepiride was to be titrated. After a starting dose of 1 mg/day, dose steps of 2, 4, and 6 mg/day and – if approved in the respective country – 8 mg/day were envisaged (dose levels 1 to 5) for titration in the glimepiride arm. To maintain blinding, the randomized study medication was also made available in the levels 1 to 5 for sham titration in both canagliflozin arms. Each level corresponded to 100 mg/day or 300 mg/day of canagliflozin. The dose level was to be increased if at least 50% of fasting plasma glucose measurements were above a target value of 110 mg/dL during the 2 weeks preceding the study visit/titration (at least 3 measurements were recommended). The interval between 2 dose level increases could be reduced to less than one week if a patient had higher blood glucose levels and the conditions for increasing the dose level were fulfilled. The dose level was not to be increased if, during the 2 weeks preceding the study visit, hypoglycaemias had occurred that, from the investigator's point of view, excluded an increase of the dose level.

Hence in the DIA3009 study, there were relevant differences between the treatment arms with regard to the specified target blood glucose levels and the therapeutic strategies determined by them. In the canagliflozin arms of the study, target blood glucose levels could not be aimed at by dose adaptation ("titration" to target levels was performed without dose changes and merely to maintain blinding) and fixed dosage was used. In the glimepiride arm, in contrast,

titration was specified by an algorithm and orientated towards near-normal target levels. The substantial differences in blood-glucose lowering between the treatment groups in the first weeks of the study were apparently induced by the one-sided possibility of reaching target levels for glimepiride. The time course of the occurrence of the key outcomes of the DIA3009 study (hypoglycaemias) corresponded to the course of blood glucose lowering. The results of the DIA3009 study could not be used for assessing the added benefit of canagliflozin/metformin versus the ACT specified by the G-BA because it remained unclear whether the observed effects are attributable to the drugs or to the therapeutic strategy. Further information on the design of the study and the influence of the different therapeutic strategies in the treatment arms on the observed effects can be found in dossier assessment A14-12 and in the addendum to commission A14-12 (A14-24) [3,4].

Moreover, almost all patients (approximately 95%) of the DIA3009 study received a metformin dose above 2000 mg. According to the SPC [5], the dose of canagliflozin/metformin is to be determined individually without exceeding the maximum recommended oral daily dose of 300 mg canagliflozin and 2000 mg metformin. According to the company, this wording was included in the SPC in the framework of the central approval process to avoid overdosing of the drug canagliflozin. From the point of view of the company, this does not mean that the total daily metformin dose is limited to 2000 mg. As the study could not be used for the benefit assessment already for the reasons explained above, the company's rationale on the relevance of the metformin dose is not further commented on. Further points in the DIA3009 study (e.g. use of canagliflozin in a starting dose of 100 mg/day without the possibility of dose increase or the use of a starting dose of 300 mg/day) are not discussed because they were not primarily relevant for the exclusion of the study.

Study DIA3006

The DIA3006 study was a randomized, double-blind, 4-arm approval study sponsored by the company with a duration of 52 weeks. Adult patients with type 2 diabetes mellitus who did not achieve adequate glycaemic control despite metformin treatment were enrolled in the study. The study compared administration of canagliflozin (in the 2 dosages of 100 mg and 300 mg/day) with sitagliptin (100 mg/day) and with placebo; the patients in the placebo arm also received sitagliptin after 26 weeks, however. Metformin was to be maintained in a dose specified by the protocol in all 4 treatment arms during the entire course of the study.

The DIA3006 study allowed no conclusions on the comparison of canagliflozin/metformin with the ACT (sulfonylureas [glibenclamide, glimepiride] plus metformin) and was therefore unsuitable for deriving an added benefit of canagliflozin/metformin.

The exclusion of the DIA3006 study deviated from the company's approach. From the company's point of view, there is a specific patient population for which treatment with sulfonylureas is unsuitable because of the - from the company's point of view - increased risk of hypoglycaemia of the sulfonylureas. The company named sitagliptin plus metformin as

alternative comparator therapy for this patient population. For the present benefit assessment however, patients who cannot be treated with sulfonylureas are considered to be an irrelevant subpopulation in the therapeutic indication (see Section 2.7.2.1 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 4A, Sections 4.2.2 and 4.2.3 of the dossier, and in Section 2.7.2.2 of the full dossier assessment.

2.3.1.1 Results on added benefit

The company presented no relevant data for research question A. Hence the added benefit of canagliflozin/metformin versus the ACT (sulfonylurea [glibenclamide, glimepiride] plus metformin) is not proven.

2.3.1.2 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 canagliflozin/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 deviates from the company's assessment, which claimed proof of a considerable added benefit. Moreover, the company claimed proof of a minor added benefit of canagliflozin/metformin in comparison with its alternative comparator therapy (sitagliptin plus metformin) for the patient population for which, from the company's point of view, sulfonylurea plus metformin is not an option.

2.3.2 List of included studies

Not applicable as the company did not present any relevant studies in the dossier, from which an added benefit of canagliflozin/metformin versus the ACT specified by the G-BA could be derived.

2.4 Research question B: canagliflozin/metformin plus sulfonylurea

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 lists on canagliflozin/metformin (studies completed up to 19 May 2014)
- bibliographical literature search on canagliflozin (last search on 16 May 2014)
- search in trial registries for studies on canagliflozin (last search on 21 May 2014)
- bibliographical literature search on the ACT (last search on 15 May 2014)
- search in trial registries for studies on the ACT (last search on 16 May 2014)

The company identified the 2 studies DIA3002 and DIA3010. These were placebo-controlled approval studies sponsored by the company, with patients with inadequate glycaemic control under prior therapy with metformin and sulfonylurea (DIA3002) or under their prior antidiabetic therapy (DIA3010). In addition to their pretreatment, patients received canagliflozin at a fixed daily dose of 100 mg or 300 mg, or placebo.

Both studies (DIA3002 and DIA3010) allowed no direct comparison of canagliflozin/metformin plus sulfonylureas with human insulin plus metformin. Hence the 2 studies were not used in the present benefit assessment to derive an added benefit of canagliflozin/metformin plus sulfonylureas versus the ACT specified by the G-BA.

This concurs with the company's approach. The company presented the study and patient characteristics and the risk of bias at study level for both studies at first. However, in the further discussion it pointed out that these were placebo-controlled studies, which were not relevant for the assessment of the added benefit of canagliflozin/metformin plus sulfonylurea.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4B, Sections 4.2.2 and 4.2.3 of the dossier, and in Section 2.7.3 of the full dossier assessment.

2.4.1.1 Results on added benefit

No relevant data were available for research question B. Hence the added benefit of canagliflozin/metformin plus sulfonylurea versus the ACT (human insulin plus metformin) is not proven. This concurs with the company's approach who claimed no added benefit for this research question.

2.4.1.2 Extent and probability of added benefit

Since no relevant studies were presented for the benefit assessment, there is no proof of an added benefit of canagliflozin/metformin plus sulfonylurea versus the ACT specified by the

G-BA (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 who claimed no added benefit for this research question.

2.4.2 List of included studies

Not applicable as the company did not present any relevant studies in the dossier, from which an added benefit of canagliflozin/metformin plus sulfonylurea versus the ACT specified by the G-BA could be derived.

2.5 Research question C: canagliflozin/metformin plus 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 lists on canagliflozin/metformin (studies completed up to 19 May 2014)
- bibliographical literature search on canagliflozin (last search on 16 May 2014)
- search in trial registries for studies on canagliflozin (last search on 21 May 2014)

The company identified no studies on the comparison of canagliflozin/metformin plus insulin versus the ACT specified by the G-BA.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4C, Sections 4.2.2 and 4.2.3 of the dossier, and in Section 2.7.4 of the full dossier assessment.

2.5.1.1 Results on added benefit

The company presented no relevant data for research question C. Hence the added benefit of canagliflozin/metformin plus insulin versus the ACT (human insulin plus metformin) is not proven. This concurs with the company's approach who claimed no added benefit for this research question.

2.5.1.2 Extent and probability of added benefit

Since no relevant studies were presented for the benefit assessment, there is no proof of an added benefit of canagliflozin/metformin plus insulin versus the ACT specified by the G-BA (human insulin plus metformin [treatment only with human insulin if metformin is not sufficiently effective]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This concurs with the company's approach who claimed no added benefit for this research question.

2.5.2 List of included studies

Not applicable as the company did not present any relevant studies in the dossier, from which an added benefit of canagliflozin/metformin plus insulin versus the ACT specified by the G-BA 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 canagliflozin/metformin in comparison with the respective ACTs specified by the G-BA is given Table 5.

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

Research question[a]	Subindication	ACT	Extent and probability of added benefit
A	Canagliflozin/metformin	Sulfonylurea (glibenclamide or glimepiride) plus metformin	Added benefit not proven
B	Canagliflozin/metformin plus sulfonylurea	Human insulin plus metformin or only human insulin if metformin is not sufficiently effective	Added benefit not proven
C	Canagliflozin/metformin plus insulin	Human insulin plus metformin or only human insulin if metformin is not sufficiently effective	Added benefit not proven
a: Designation corresponds to the coding in the company's dossier. b: The comparator therapy chosen by the company is printed in **bold**. ACT: appropriate comparator therapy			

The research questions presented by the company do not cover the entire approved therapeutic indication of canagliflozin/metformin. The company noted in the dossier that further combination therapies are approved. However, according to the company, there are no clinical data for these therapies to investigate an added benefit of canagliflozin/metformin. It therefore submitted no corresponding modules. An added benefit of these combination therapies is not proven.

The present assessment deviates from that of the company, which overall derived proof of considerable added benefit of canagliflozin/metformin versus sulfonylurea (glibenclamide, glimepiride) plus metformin for research question A. Moreover, for this subindication, the company claimed proof of a minor added benefit of canagliflozin/metformin versus the alternative comparator therapy sitagliptin plus metformin chosen by the company for a population of patients for whom, from the company's point of view, sulfonylureas are unsuitable.

The G-BA decides on the added benefit.

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Please see full dossier assessment for full reference list.

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