IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports A17-66

Dapagliflozin/metformin (type 2 diabetes mellitus) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment Dapagliflozin/Metformin *(Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 March 2018). 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 (type 2 diabetes mellitus) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

21 December 2017

Internal Commission No.:

A17-66

Address of publisher:

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Keywords: dapagliflozin, metformin, diabetes mellitus – type 2, benefit assessment, NCT02471404

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
HbA1c	haemoglobin A1c

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 IQWiG to assess the benefit of the drug combination dapagliflozin/metformin. The company submitted a first dossier on the drug combination on 15 February 2014 to be evaluated for the early benefit assessment. The company now requested a new benefit assessment for a subindication – i.e. an add-on combination therapy of dapagliflozin with metformin – because of new scientific findings. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 21 December 2017.

Research question

The aim of this report was to assess the added benefit of the fixed combination of dapagliflozin and metformin (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 therapeutic indication:

- as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximally tolerated dose of metformin alone.

The assessment was conducted in comparison with the G-BA's ACT. This ACT is shown in Table 2.

Table 2: Research question of the benefit assessment of dapagliflozin/metformin in type 2 diabetes mellitus

Subindication	**ACT**[a]
Dapagliflozin/metformin	▪ **Metformin + sulfonylurea** (glibenclamide or glimepiride)[b] or ▪ metformin + empagliflozin or ▪ metformin + liraglutide[c]
a: Presentation of the respective ACT specified by the G-BA. 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: According to the G-BA's commission, studies of direct comparison with glipizide should also be assessed. c: Liraglutide in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for operationalization, see study protocol [1]. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

In its choice of the comparator therapy, the company followed the G-BA's specification and chose metformin + sulfonylurea from the options. It additionally described that it also considered studies versus the sulfonylurea glipizide. Glipizide is not approved in Germany. According to the G-BA's commission, the comparison versus glipizide was also considered and outlined in a separate research question in the present assessment.

The benefit assessment of dapagliflozin/metformin was conducted according to the Summary of Product Characteristics (SPC) for the patient population described above and the approval-compliant daily dosage of the fixed combination (dapagliflozin: 10 mg; metformin: ≥ 1700 mg).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

The company identified the following RCTs for the assessment of the added benefit of dapagliflozin/metformin in adult patients with type 2 diabetes mellitus:

- for the comparison of dapagliflozin/metformin vs. glimepiride + metformin: study D1689C00014 (study DapaZu); this study was conducted after the first dossier assessment on dapagliflozin/metformin and submitted by the company for the present dossier assessment for the first time,
- for the comparison of dapagliflozin/metformin vs. glipizide + metformin: study D1690C00004; this study was already the subject of the first dossier assessment on dapagliflozin/metformin.

An added benefit of dapagliflozin/metformin in comparison with the ACT could be derived from neither of the two studies.

Dapagliflozin/metformin vs. glimepiride + metformin

DapaZu study

The DapaZu study is a randomized, active-controlled, double-blind phase 4 study on the comparison of dapagliflozin + metformin with glimepiride + metformin. The combination of dapagliflozin + metformin was administered in the form of single tablets (loose combination). Adult patients between 18 and 74 years with type 2 diabetes mellitus in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable, maximum tolerated dosage and who had a glycosylated haemoglobin A1c (HbA1c) value between ≥ 7.5% and ≤ 10.5% in the inclusion phase were included in the DapaZu study.

The study consisted of a 2-week inclusion phase, a treatment phase of 52 weeks and a follow-up phase of 3 weeks.

After randomization, the patients received either a fixed dose of 10 mg/day dapagliflozin or a starting dose of 1 mg/day glimepiride, each in addition to placebo, to blind the assignment to the individual study arms. At each visit, the investigator could increase the glimepiride dose by 1 mg/day up to a maximum dose of 6 mg/day (at an interval of at least 2 weeks). In addition, all patients received a stable metformin dose that had been ongoing before study inclusion.

The primary outcome of the study was the change in HbA1c after 52 weeks of treatment. The aim was to show the non-inferiority of dapagliflozin versus glimepiride (each combined with metformin) regarding the change of the HbA1c values from the start of the study to treatment week 52.

A total of 939 patients were randomly assigned to the 3 study arms dapagliflozin, glimepiride as well as dapagliflozin + saxagliptin (each in addition to metformin). Only the two study arms dapagliflozin + metformin and glimepiride + metformin were relevant for the present assessment. For the assessment of the fixed combination dapagliflozin/metformin, the company selected patients pretreated with a minimum metformin dose of 1700 mg/day. This restriction resulted from the potencies of dapagliflozin and metformin approved for the fixed combination. The subpopulation included about 88% of the patients in the total population. Assessment of the interpretability of the results on the total population thus also applies, in its entirety, to the research question on the fixed combination dapagliflozin/metformin. This assessment of the interpretability of results is described in detail in the dossier assessment on the loose combination of dapagliflozin and metformin (A17-65).

Results on hypoglycaemic events not interpretable

The results of the above described DapaZu study on the outcome “hypoglycaemia” are not interpretable. This is primarily due to the concrete blood-glucose lowering approach in the control group (active titration with glimepiride with regular dose increase up to 6 mg/day) combined with the resulting clear differences in blood-glucose lowering (no non-inferiority of dapagliflozin during the course of the study). The individually specified blood glucose treatment goals were also achieved less frequently under dapagliflozin, whereby, moreover, the determination of the treatment goals remained unclear on the basis of the documents presented by the company.

If, irrespective of the issues mentioned above, the results of the DapaZu study were considered in detail, they altogether show no advantage of dapagliflozin/metformin versus glimepiride.

Dapagliflozin/metformin vs. glipizide + metformin

Study D1690C00004

The study D1690C00004 is a randomized, double-blind and active-controlled approval study on the comparison of dapagliflozin + metformin with glipizide + metformin. The company already presented this study for the first assessment of dapagliflozin as single agent (A12-18 and A13-18) and as fixed combination with metformin (A14-07), which is extensively described there. In its elaboration on the benefit assessment decisions for dapagliflozin as well as the fixed combination dapagliflozin/metformin, the G-BA explained in detail why an added benefit of dapagliflozin/metformin cannot be derived from study D1690C00004. Moreover, it includes no new scientific findings for the current assessment. Detailed explanations for the non-relevance of the study are found in the mentioned first assessments.

Summary

The data presented by the company provided no hint of an added benefit of dapagliflozin/metformin in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 presents a summary of the probability and extent of the added benefit of dapagliflozin/metformin.

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

Subindication	ACT[a]	Probability and extent of added benefit
Dapagliflozin/metformin	▪ **Metformin + sulfonylurea** (glibenclamide or glimepiride)[b] or ▪ metformin + empagliflozin or ▪ metformin + liraglutide[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. 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: According to the G-BA's commission, studies of direct comparison with glipizide should also be assessed.
c: Liraglutide in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for operationalization, see study protocol [1]).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [2,3].

2.2 Research question

The aim of this report was to assess the added benefit of the fixed combination of dapagliflozin and metformin (dapagliflozin/metformin) for the treatment of adult patients with type 2 diabetes mellitus in comparison with the ACT in the following approved therapeutic indication:

- as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximally tolerated dose of metformin alone.

Dapagliflozin/metformin is also approved for the combination therapy with other blood-glucose lowering drugs. This indication is not subject of the present assessment. The assessment was conducted in comparison with the G-BA's ACT. This ACT is shown in Table 4.

Table 4: Research question of the benefit assessment of dapagliflozin/metformin in type 2 diabetes mellitus

Subindication	**ACT**[a]
Dapagliflozin/metformin	▪ **Metformin + sulfonylurea** (glibenclamide or glimepiride)[b] or ▪ metformin + empagliflozin or ▪ metformin + liraglutide[c]
a: Presentation of the respective ACT specified by the G-BA. 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: According to the G-BA's commission, studies of direct comparison with glipizide should also be assessed. c: Liraglutide in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for operationalization, see study protocol [1]). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

In its choice of the comparator therapy, the company followed the G-BA's specification and chose metformin + sulfonylurea from the options. It additionally stated that it also considered studies in comparison with the sulfonylurea glipizide. Glipizide is not approved in Germany. According to the G-BA's commission, the comparison versus glipizide was also considered and outlined in a separate research question in the present assessment.

The benefit assessment of dapagliflozin/metformin was conducted according to the SPC for the patient population described above and the approval-compliant daily dosage of the fixed combination (dapagliflozin: 10 mg; metformin: ≥ 1700 mg).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on dapagliflozin (status: 17 October 2017)
- bibliographical literature search on dapagliflozin (last search on 17 October 2017)
- search in trial registries for studies on dapagliflozin (last search on 16 October 2017)

To check the completeness of the study pool:

- search in trial registries for studies on dapagliflozin (last search on 11 January 2018)

The check identified no additional relevant study.

The company identified the following RCTs for the assessment of the added benefit of dapagliflozin/metformin in adult patients with type 2 diabetes mellitus, which were also presented for the assessment of the loose combination dapagliflozin + metformin [4]:

- for the comparison of dapagliflozin/metformin vs. glimepiride + metformin: study D1689C00014 (study DapaZu) [5-7]; this study was conducted after the first dossier assessment on dapagliflozin/metformin (dossier assessment A14-07) and submitted by the company for the present dossier assessment for the first time,
- for the comparison of dapagliflozin/metformin vs. glipizide + metformin: study D1690C00004 [8]; this study was already the subject of the first dossier assessment on dapagliflozin/metformin.

Both RCTs are presented in Table 5.

Table 5: Study pool of the company – RCT, direct comparison: dapagliflozin/metformin vs. sulfonylurea + metformin

Study	**Study category**		
	Study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
D1689C00014 (DapaZu[b])	No	Yes	No
D1690C00004	Yes	Yes	No
a: Study sponsored by the company. b: Hereinafter, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

An added benefit of dapagliflozin/metformin in comparison with the ACT could not be derived from the two studies included by the company. This is explained below.

Dapagliflozin/metformin vs. glimepiride + metformin

DapaZu study

Study characteristics

Table 6 and Table 7 describe the DapaZu study.

Table 6: Characteristics of the DapaZu study included by the company – RCT, direct comparison: dapagliflozin + metformin vs. glimepiride + metformin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
DapaZu	RCT, double-blind, parallel	Adult patients (18 to 74 years) with type 2 diabetes mellitus and HbA1c of ≥ 7.5% to ≤ 10.5% with prior metformin treatment with a maximum tolerated dose of ≥ 1500[d] mg/day for at least 8 weeks	▪ Dapagliflozin + placebo (for saxagliptin + glimepiride) + metformin (N = 314) ▪ Glimepiride + placebo (for dapagliflozin + saxagliptin) + metformin (N = 313) ▪ Dapagliflozin + saxagliptin + placebo (for glimepiride) + metformin (N = 312)[c] <u>Approval-compliant subpopulation</u>: pretreated with ≥ 1700 mg/day metformin ▪ Dapagliflozin + placebo (for saxagliptin + glimepiride) + metformin (N = 283) ▪ Glimepiride + placebo (for dapagliflozin + saxagliptin) + metformin (N = 268)	Screening: 1 week Inclusion phase: 2 weeks Treatment phase: 52 weeks Follow-up: 3 weeks[b]	194 study centres in Czech Republic, Germany, Hungary, Poland and Slovakia, 09/2015-03/2017	Primary: change in HbA1c after 52 weeks of treatment Secondary: morbidity, hypoglycaemic events, health-related quality of life, side effects

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain information on relevant available outcomes from the information provided by the company in Module 4 A of the dossier.
b: Applies to adverse events (up to and including 4 days in case of AEs and at most 30 days in case of SAEs after administration of the last dose of the study medication).
c: The arm is not relevant for the assessment and is no longer shown in the following tables.
d: Only patients pretreated with ≥ 1700 mg/day metformin were in compliance with the approval of dapagliflozin/metformin.
AE: adverse event; HbA1c: haemoglobin A1c; N: number of randomized patients; n = number of randomized patients in the approval-compliant subpopulation; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: dapagliflozin + metformin vs. glimepiride + metformin

Study	Intervention	Comparison
DapaZu	▪ Dapagliflozin 10 mg, once daily, orally + metformin ≥ 1500 mg/day[a], orally, at current dosage + placebo for saxagliptin + placebo for glimepiride	▪ Glimepiride (starting dose 1 mg, titration up to 6 mg), once daily, orally + metformin ≥ 1500 mg/day[a], orally, at current dosage + placebo for dapagliflozin + placebo for saxagliptin *Titration/dose increase of glimepiride* Starting dose: 1 mg/day Dose increase by 1 mg every 2 weeks up to a maximum dose of 6 mg/day was possible. Individual target value, a fasting plasma glucose (FPG) target value of about 110 mg/dl was recommended. Dose reduction was allowed.
	Prior and concomitant medication *Pretreatment* Pretreatment for at least 8 weeks before the start of the study with metformin ≥ 1500 mg/day[a] i.e. in a maximum tolerated dose *Non-permitted concomitant treatment* ▪ Sulfonylureas, pioglitazone, rosiglitazone, GLP-1 receptor agonists, dipeptidyl-peptidase-4 (DPP-4) and Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors, loop diuretics ▪ further test medication ▪ systemic glucocorticoids (equivalent to ≥ 10 mg/day oral prednisolone) ≥ 5 days (inhalation and topical application were allowed) ▪ over-the-counter drugs for weight reduction *As-needed medication* Glycaemic rescue medication with insulin was allowed within a defined range of FPG or HBA1c threshold values for a total of 14 days and for up to 7 consecutive days: ▪ weeks 0 to 12 (after visit 2 and including visit 8): FPG > 240 mg/dl (13.3 mmol/l) ▪ weeks 12 to 24 (after visit 8 and including visit 9): FPG > 200 mg/dl (11.1 mmol/l) ▪ weeks 24 to 52 (after visit 9 and including visit 12): HbA1c > 8.0 %	

a: For the approval-compliant subpopulation metformin ≥ 1700 mg/day.
DPP-4: dipeptidyl-peptidase-4; FPG: Fasting Plasma Glucose; GLP-1: glucagon-like-peptide-1; HbA1c: haemoglobin A1c; RCT: randomized controlled trial; SGLT2: Sodium Glucose Co-Transporter 2; vs.: versus

The DapaZu study is a randomized, active-controlled, double-blind phase 4 study on the comparison of dapagliflozin + metformin with glimepiride + metformin. The combination of dapagliflozin + metformin was administered in the form of single tablets (loose combination).

Adult patients between 18 and 74 years with type 2 diabetes mellitus in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable, maximum

tolerated dosage and who had an HbA1c value between ≥ 7.5% and ≤ 10.5% in the inclusion phase were included in the DapaZu study. All patients should have received metformin at a stable dosage of ≥ 1500 mg/day for at least 8 weeks before inclusion. The study consisted of a 2-week inclusion phase, a treatment phase of 52 weeks and a follow-up phase of 3 weeks.

After randomization, the patients received either a fixed dose of 10 mg/day dapagliflozin or a starting dose of 1 mg/day glimepiride, each in addition to placebo, to blind the assignment to the individual study arms. At each visit, the investigator could increase the glimepiride dose by 1 mg/day up to a maximum dose of 6 mg/day (at an interval of at least 2 weeks). In addition, all patients received a stable metformin dose that had been ongoing before study inclusion. Hyperglycaemic rescue medication with insulin was allowed in addition to the randomized study medication and metformin within the defined glucose threshold values after the maximum glimepiride dose (6 mg/day) or glimepiride-placebo dose had been reached (see Table 7).

The primary outcome of the study was the change in HbA1c after 52 weeks of treatment. The aim was to show the non-inferiority of dapagliflozin versus glimepiride (each combined with metformin) regarding the change of the HbA1c values from the start of the study to treatment week 52 (see Table 6).

A total of 939 patients were randomly assigned to the 3 study arms dapagliflozin, glimepiride as well as dapagliflozin + saxagliptin (each in addition to metformin). Only the two study arms dapagliflozin + metformin and glimepiride + metformin were relevant for the present assessment. For the assessment of the fixed combination dapagliflozin/metformin, the company selected patients pretreated with a minimum metformin dose of 1700 mg/day (see Table 6). This restriction resulted from the potencies of dapagliflozin and metformin approved for the fixed combination. [9]. The subpopulation included 90.1% (283 of 314) of the patients in the intervention arm and 85.6% (268 of 313) of the patients in the comparator arm (see Table 6) and thus amounts to about 88% of the total population. Assessment of the interpretability of the results on the total population thus also applies, in its entirety, to the research question on the fixed combination dapagliflozin/metformin. This assessment of the interpretability of results is described in detail in the dossier assessment on the loose combination of dapagliflozin and metformin (A17-65) [4].

Results on hypoglycaemic events not interpretable

The results of the above described DapaZu study on the outcome “hypoglycaemic events” are not interpretable. This is primarily due to the concrete blood-glucose lowering approach in the control group (active titration with glimepiride with regular dose increase up to 6 mg/day) combined with the resulting clear differences in blood-glucose lowering (no non-inferiority of dapagliflozin during the course of the study). The individually specified blood glucose treatment goals were also achieved less frequently under dapagliflozin, whereby, moreover, the determination of the treatment goals remained unclear on the basis of the documents presented by the company.

If, irrespective of the issues mentioned above, the results of the DapaZu study were considered in detail, they altogether showed no advantage of dapagliflozin/metformin versus glimepiride.

A detailed presentation of the reasons for the non-interpretability is found in benefit assessment A17-65 on dapagliflozin + metformin (loose combination) [4].

The results on the subpopulation (≥ 1700 mg/day metformin) are also provided in Appendix A as a supplementary information.

Dapagliflozin/metformin vs. glipizide + metformin

Study D1690C00004

The study D1690C00004 is a randomized, double-blind and active-controlled approval study on the comparison of dapagliflozin + metformin with glipizide + metformin sponsored by the company. The company already presented this study for the first assessment of dapagliflozin as single agent (A12-18 and A13-18) [10,11] and as fixed combination with metformin (A14-07) [12], which is extensively described there.

In its elaboration on the benefit assessment decisions for dapagliflozin and for the fixed combination dapagliflozin/metformin, the G-BA explained in detail why an added benefit of dapagliflozin/metformin cannot be derived from study D1690C00004 [13,14]. Since study D1690C00004 already ended in 2013, the data for the analysis time point of 208 weeks presented by the company for the present benefit assessment were already available for the first assessment of the fixed combination dapagliflozin/metformin. Therefore, they provide no new scientific findings for the current assessment.

2.4 Results on added benefit

The data presented by the company provided no hint of an added benefit of dapagliflozin/metformin in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of dapagliflozin/metformin in comparison with the ACT is presented in Table 8.

Table 8: Dapagliflozin/metformin – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Dapagliflozin/metformin	▪ **Metformin + sulfonylurea** (glibenclamide or glimepiride)[b] or ▪ metformin + empagliflozin or ▪ metformin + liraglutide[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. 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: According to the G-BA's commission, studies of direct comparison with glipizide should also be assessed.
c: Liraglutide in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for operationalization, see study protocol [1]).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.6 List of included studies

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

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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