IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-33

Saxagliptin/metformin (type 2 diabetes mellitus) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Saxagliptin/Metformin (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 October 2017). 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.

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Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the fixed combination of saxagliptin and metformin (saxagliptin/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 21 July 2017.

Research question

The aim of the present report was to assess the added benefit of the fixed combination of saxagliptin and metformin (saxagliptin/metformin) in adult patients with type 2 diabetes mellitus in the following subindication in accordance with the extension of the therapeutic indication approved in June 2017:

- saxagliptin/metformin in combination with other medicinal products for the treatment of diabetes (except insulin and sulfonylurea) (as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled with metformin and these medicinal products)

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 saxagliptin/metformin in type 2 diabetes mellitus

Subindication	**ACT[a]**
Saxagliptin/metformin plus other drugs for the treatment of diabetes (except insulin and sulfonylurea)	▪ **Human insulin[b] plus metformin** or ▪ human insulin plus empagliflozin[c] or ▪ human insulin if, according to the SPC, metformin and empagliflozin are unsuitable or not sufficiently effective due to intolerance or contraindication

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: Deviating from the G-BA's specification, the company chose insulin (including insulin analogues) plus metformin as comparator therapy. This deviation was not followed (see Section 2.7.1 of the full dossier assessment).
c: 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, operationalized in the EMPA-REG-Outcome study as at least 1 of the following conditions: confirmed myocardial infarction, clinically relevant single-vessel coronary artery disease with ≥ 50% stenosis, multi-vessel coronary artery disease, unstable angina with angiographic confirmation of coronary heart disease, ischaemic or haemorrhagic stroke or peripheral artery disease with clinically relevant ischaemia (see study protocol, [3]).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

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

Results

The company did not present any data for the assessment of the added benefit of saxagliptin/metformin in combination with other drugs (except insulin and sulfonylureas) versus the appropriate comparator therapy (ACT). Hence there was no hint of an added benefit of saxagliptin/metformin in combination with other drugs (except insulin and sulfonylureas) in comparison with the ACT specified by the G-BA; an added benefit is therefore not proven.

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

The result of the assessment of the added benefit of saxagliptin/metformin in combination with other drugs (except insulin and sulfonylureas) in comparison with the ACT is presented in Table 3.

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

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

Subindication	ACT[a]	Probability and extent of added benefit
Saxagliptin/metformin plus other drugs for the treatment of diabetes (except insulin and sulfonylurea)	▪ **Human insulin[b] plus metformin** or ▪ human insulin plus empagliflozin[c] or ▪ human insulin if, according to the SPC, metformin and empagliflozin are unsuitable or not sufficiently effective due to intolerance or contraindication	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: Deviating from the G-BA's specification, the company chose insulin (including insulin analogues) plus metformin as comparator therapy. This deviation was not followed (see Section 2.7.1 of the full dossier assessment).
c: 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, operationalized in the EMPA-REG-Outcome study as at least 1 of the following conditions: confirmed myocardial infarction, clinically relevant single-vessel coronary artery disease with ≥ 50% stenosis, multi-vessel coronary artery disease, unstable angina with angiographic confirmation of coronary heart disease, ischaemic or haemorrhagic stroke or peripheral artery disease with clinically relevant ischaemia (see study protocol, [3]).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of the fixed combination of saxagliptin and metformin (saxagliptin/metformin) in adult patients with type 2 diabetes mellitus in the following subindication in accordance with the extension of the therapeutic indication approved in June 2017:

- saxagliptin/metformin in combination with other medicinal products for the treatment of diabetes (except insulin and sulfonylurea) (as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled with metformin and these medicinal products)

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 saxagliptin/metformin in type 2 diabetes mellitus

Subindication	**ACT**[a]
Saxagliptin/metformin plus other drugs for the treatment of diabetes (except insulin and sulfonylurea)	▪ **Human insulin**[b] **plus metformin** or ▪ human insulin plus empagliflozin[c] or ▪ human insulin if, according to the SPC, metformin and empagliflozin are unsuitable or not sufficiently effective due to intolerance or contraindication
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: Deviating from the G-BA's specification, the company chose insulin (including insulin analogues) plus metformin as comparator therapy. This deviation was not followed (see Section 2.7.1 of the full dossier assessment). c: 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, operationalized in the EMPA-REG-Outcome study as at least 1 of the following conditions: confirmed myocardial infarction, clinically relevant single-vessel coronary artery disease with ≥ 50% stenosis, multi-vessel coronary artery disease, unstable angina with angiographic confirmation of coronary heart disease, ischaemic or haemorrhagic stroke or peripheral artery disease with clinically relevant ischaemia (see study protocol, [3]). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics	

Deviating from this, the company also named the combination of saxagliptin/metformin with sulfonylureas as part of the research question. However, the present assessment only comprised the extension of the therapeutic indication of saxagliptin/metformin from June 2017 with combinations with other medicinal products for the treatment of diabetes, except insulin and sulfonylurea. Combinations with insulin and with sulfonylurea were already approved in October 2012 and February 2013 and were then assessed [4-6]. Deviating from the company, the present assessment only considered the part of the therapeutic indication of saxagliptin/metformin that comprised the extension of the therapeutic indication (see Section 2.7.2.1 of the full dossier assessment).

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 saxagliptin/metformin plus other drugs for the treatment of diabetes (except insulin and sulfonylurea) (status: 8 June 2017)

- bibliographical literature search on saxagliptin/metformin plus other drugs for the treatment of diabetes (except insulin and sulfonylurea) (last search on 9 June 2017)
- search in trial registries for studies on saxagliptin/metformin plus other drugs for the treatment of diabetes (except insulin and sulfonylurea) (last search on 8 June 2017)

To check the completeness of the study pool:

- search in trial registries for studies on saxagliptin/metformin plus other drugs for the treatment of diabetes (except insulin and sulfonylurea) (last search on 14 August 2017)

No relevant study was identified from the check.

The company also identified no relevant study for the present benefit assessment.

2.4 Results on added benefit

The company did not present any data for the assessment of the added benefit of saxagliptin/metformin in combination with other drugs for the treatment of diabetes (except insulin and sulfonylureas) versus the ACT. Hence there was no hint of an added benefit of saxagliptin/metformin in comparison with the ACT specified by the G-BA; 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 saxagliptin/metformin in combination with other drugs for the treatment of diabetes (except insulin and sulfonylureas) in comparison with the ACT is presented in Table 5.

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

Subindication	ACT[a]	Probability and extent of added benefit
Saxagliptin/metformin plus other drugs for the treatment of diabetes (except insulin and sulfonylurea)	▪ **Human insulin[b] plus metformin** or ▪ human insulin plus empagliflozin[c] or ▪ human insulin if, according to the SPC, metformin and empagliflozin are unsuitable or not sufficiently effective due to intolerance or contraindication	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: Deviating from the G-BA's specification, the company chose insulin (including insulin analogues) plus metformin as comparator therapy. This deviation was not followed (see Section 2.7.1 of the full dossier assessment).
c: 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, operationalized in the EMPA-REG-Outcome study as at least 1 of the following conditions: confirmed myocardial infarction, clinically relevant single-vessel coronary artery disease with ≥ 50% stenosis, multi-vessel coronary artery disease, unstable angina with angiographic confirmation of coronary heart disease, ischaemic or haemorrhagic stroke or peripheral artery disease with clinically relevant ischaemia (see study protocol, [3]).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The assessment described above concurs with that of the company, which also derived no added benefit of saxagliptin/metformin in combination with other drugs for the treatment of diabetes (except insulin and sulfonylureas) in comparison with the ACT.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no 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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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-33-saxagliptin-metformin-type-2-diabetes-benefit-assessment-according-to-35a-social-code-book-v.7933.html.