IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Saxagliptin/metformin – Benefit assessment according to § 35a Social Code Book V[1]

Extract

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
DPP-4	dipeptidyl-peptidase 4
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)
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 fixed combination of saxagliptin and metformin. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 15.11.2012.

Research question

The benefit assessment of the fixed combination of saxagliptin and metformin was conducted in accordance with its approval status for the following therapeutic indications:

- **Combination of saxagliptin and metformin:** "as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets" [3]
- **Combination of saxagliptin and metformin in combination with insulin**: (i.e., triple combination therapy) "as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control" [3]

Combination of saxagliptin and metformin

For the therapeutic indication "saxagliptin plus metformin", the G-BA specified the following appropriate comparator therapy (ACT):

- Metformin in combination with a sulfonylurea (glibenclamide or glimepiride)

The company also cited metformin in combination with a sulfonylurea as ACT for this therapeutic indication, but without limitation to the drugs glibenclamide and glimepiride specified by the G-BA. It pointed out that the added benefit was to be derived on the basis of an approval study where the sulfonylurea glipizide had been used. However, as the company itself noted in its dossier, glipizide has not been approved in Germany since 2007 and is therefore unsuitable as ACT. Furthermore, the company justified the admissibility of a comparison with glipizide, instead of glibenclamide or glimepiride, particularly with the comparability of glipizide with these drugs. However, the data presented by the company were insufficient to support this assumption made by the company. In addition, the company cited the combination therapy of metformin plus other DPP-4 inhibitors as an alternative comparator therapy, namely for patients who cannot be treated with sulfonylurea or for whom sulfonylurea is unsuitable, but insulin therapy is not yet indicated. According to the

information given by the company, this limitation of the patient population mainly refers to hypoglycaemias, the adverse event most commonly observed during treatment with sulfonylureas. Regarding this, the company cited several risk factors such as advanced age and pre-existing cardiovascular conditions. This rationale was not followed. According to the Summary of Product Characteristics (SPC) for glibenclamide there are no contraindications for the patient groups named by the company. Regarding elderly people it is pointed out that particular caution should be exercised when adjusting the dose; this does not mean however that sulfonylureas are unsuitable for these patients. Hence the company did not exclude elderly patients from the direct comparative study with glipizide. Patients with recent pre-existing cardiovascular conditions were excluded from the study, but this also applied to the placebo-controlled studies on saxagliptin, where sulfonylureas were not used at all. Moreover, the company did not submit any data to prove an added benefit of saxagliptin plus metformin versus the alternative ACT sitagliptin plus metformin the company had chosen.

In summary, the assessment was conducted for the therapeutic indication "saxagliptin plus metformin" in comparison with the ACT specified by the G-BA "metformin plus sulfonylurea (glibenclamide or glimepiride)".

Combination of saxagliptin and metformin in combination with insulin

Due to the lack of a consultation request, the G-BA had not specified an ACT in advance for the therapeutic indication "saxagliptin plus metformin in combination with insulin". However, the company followed the ACT specified by the G-BA after explanations by the company during a consultation request for the individual substance saxagliptin for the same therapeutic indication:

- Metformin + human insulin

This assessment followed the G-BA's specification for the individual substance and therefore the company's choice.

The assessment for both therapeutic indications was conducted based on patient-relevant outcomes.

Results

Combination of saxagliptin and metformin

The company did not submit any direct comparative studies on the combination of saxagliptin and metformin versus the ACT specified by the G-BA (metformin and sulfonylurea [glibenclamide or glimepiride]). The only study the company included in the assessment was D1680C00001, which compared the (free) combination of saxagliptin plus metformin with glipizide plus metformin. The company named the equivalence of glipizide with glimepiride or glibenclamide as a key argument for including this study. To prove the equivalence, the company conducted a search in bibliographical databases for randomized controlled trials (RCTs) that compared glipizide with glimepiride or glibenclamide. The company summarized

the 5 studies identified in a meta-analysis, but data were available for only a few of the outcomes considered by the company, and not for all of the 5 studies, either. Because from the company's point of view there was no statistically significant difference between glipizide and glibenclamide regarding efficacy and safety, the company considered the equivalence as confirmed.

The basic approach of the company to search for relevant studies to prove the equivalence of glipizide with glimepiride or glibenclamide is comprehensible. But the company's search for these studies was already incomplete due to limitations of the search period to the years 1991 to 2011. The Institute's orientation search for the period before 1991 and for the year 2012 found 2 additional studies – also exclusively on the comparison of glipizide with glibenclamide. Moreover, 3 of the 5 studies identified by the company were too short (< 24 weeks) to prove the equivalence of the sulfonylureas. The equivalence of glipizide with glibenclamide or glimepiride could not be proven on the basis of the remaining 4 studies (nor on the basis of the 5 studies originally included by the company). 3 of the 4 studies included patients at an early stage of the disease (i.e., patients with insufficient glycaemic control on diet and/or without previous drug treatment). However, the combination of saxagliptin and metformin is only approved for patients at an advanced stage (insufficient control with metformin or previous treatment with a combination of saxagliptin and metformin as separate tablets). With one exception, the 4th study included patients with previous insulin therapy, and in the study itself sulfonylureas were given as monotherapy, but not in combination with metformin. The company did not submit proof of the applicability of the results to the approval-compliant patient population. Regardless of this, all studies showed (an at least numerically) greater reduction of blood glucose under glibenclamide than under glipizide (e.g. HbA1(c) values at the end of the study: 5.76% under glipizide versus 5.13% under glibenclamide, and 11% under glipizide versus 9% under glibenclamide), which rather led to an indication of lack of equivalence of the two drugs.

The company included a meta-analysis on saxagliptin (as monotherapy or combination therapy with other oral antidiabetics) as another investigation with the goal of assessing the occurrence of cardiovascular events under saxagliptin therapy. The company also cited an – according to the company – indirect comparison of this meta-analysis with 2 further systematic reviews with sulfonylureas (alone or in combination with metformin). It used other blood-glucose-lowering therapies as a "common intermediate comparator". This approach of the company was unsuitable for proving an added benefit of saxagliptin plus metformin versus the ACT.

Combination of saxagliptin and metformin in combination with insulin

The company submitted a direct comparative study (CV181057) for the therapeutic indication "saxagliptin plus metformin in combination with insulin". This study was not suitable for assessing the added benefit, as in the study it was prohibited to adapt the insulin therapy to individual necessities in the first treatment phase, particularly in the comparator group.

Study CV181057 included patients who had received previous therapy with insulin (plus metformin if necessary) that had been inadequate. The study consisted of a run-in phase and 2 treatment phases.

In the first treatment phase (24 weeks, stable insulin phase), basic therapy (insulin, plus metformin if necessary) was to remain unchanged, i.e., neither the type of insulin nor the kind of insulin therapy (e.g. basal-supported oral therapy) was permitted to be changed. Changing to a flexible therapy was only allowed when the criteria for emergency treatment were met. Moreover, possible adjustments of the insulin dose had to be discussed with the investigator, who was, however, to encourage the patients to maintain their insulin dose. Due to the specifications of the study design, this treatment phase was unsuitable for drawing conclusions on the added benefit of the combination of saxagliptin and metformin in combination with insulin versus the ACT specified by the G-BA.

In the flexible insulin phase (no new randomization, 28 weeks), the patients' therapy from the first treatment phase was continued. In contrast to the first treatment phase, insulin dosage and the type of insulin administered could be changed individually in both treatment arms. However, it was unclear according to which criteria a change to a different type of insulin was performed, and whether changing the type of insulin and, if necessary, the insulin regimen, was accompanied by an adequate patient education course. Moreover, because at this point the patients in the intervention arm had already been treated with saxagliptin for 24 weeks, while the patients in the comparator arm had received no optimization of their previous treatment, the intervention and control group no longer had the same conditions when the second treatment phase started. Overall, the results of the second treatment phase and thus the entire study CV181057 could not be used for assessing the added benefit.

Summary

There were no relevant data for either therapeutic indication in the dossier. Hence there is no proof for either therapeutic indication of an added benefit of the combination of saxagliptin and metformin versus the respective ACT specified by the G-BA.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the extent and probability of the added benefit of the combination of saxagliptin and metformin and the combination of saxagliptin and metformin in combination with insulin compared with the ACT are assessed as follows:

Combination of saxagliptin and metformin

There is no proof of an added benefit of the combination of saxagliptin and metformin compared with the ACT specified by the G-BA. As a result, there are no patient groups for whom a therapeutically important added benefit can be derived.

Combination of saxagliptin and metformin in combination with insulin

There is no proof of an added benefit of the combination of saxagliptin and metformin in combination with insulin compared with the ACT specified by the G-BA. As a result, there are no patient groups for whom a therapeutically important added benefit can be derived.

The decision on added benefit is made by the G-BA.

2.2 Research question

The benefit assessment of the fixed combination of saxagliptin and metformin (saxagliptin/metformin) was conducted in accordance with its approval status [3] for the following therapeutic indications:

- **Combination of saxagliptin and metformin:** "as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets" [3]
- **Combination of saxagliptin and metformin in combination with insulin**: (i.e., triple combination therapy) "as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control" [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 1-3 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].

Combination of saxagliptin and metformin

For the therapeutic indication "saxagliptin plus metformin", the G-BA specified the following ACT:

- Metformin in combination with a sulfonylurea (glibenclamide or glimepiride)

The company also cited metformin in combination with a sulfonylurea as ACT for this therapeutic indication, but without limitation to the drugs glibenclamide and glimepiride specified by the G-BA. It pointed out that the added benefit was to be derived on the basis of an approval study where the sulfonylurea glipizide had been used. As the company itself noted in its dossier, glipizide has not been approved in Germany since 2007, however, and is therefore unsuitable as ACT. Furthermore, the company justified the admissibility of a comparison with glipizide instead of glibenclamide or glimepiride particularly with the comparability of glipizide with these drugs. However the data presented by the company were insufficient to support this assumption made by the company. Further information on this can be found in Section 2.7.1 of the full dossier assessment.

In addition, the company cited the combination therapy of metformin plus other DPP-4 inhibitors as an alternative comparator therapy, namely for patients who cannot be treated with sulfonylurea or for whom sulfonylurea is unsuitable, but insulin therapy is not yet indicated. According to the information given by the company, this limitation of the patient population mainly refers to hypoglycaemias, the adverse event most commonly observed during treatment with sulfonylureas. This rationale was not followed. Further information on this can be found in Section 2.7.1 of the full dossier assessment.

In summary, the assessment was conducted for the therapeutic indication "saxagliptin plus metformin" in comparison with the ACT specified by the G-BA "metformin plus sulfonylurea (glibenclamide or glimepiride)".

Combination of saxagliptin and metformin in combination with insulin

Due to the lack of a consultation request, the G-BA had not specified an ACT in advance for the therapeutic indication "saxagliptin plus metformin in combination with insulin". However, the company followed the ACT specified by the G-BA after explanations by the company during a consultation request for the individual substance saxagliptin for the same therapeutic indication:

- Metformin + human insulin

This assessment followed the G-BA's specification and therefore followed the company's choice.

The assessment for both therapeutic indications was conducted based on patient-relevant outcomes.

Further information on the research question can be found in Module 3, Section 3B and in Module 4A and 4B, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

Combination of saxagliptin and metformin

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

- Studies on metformin plus saxagliptin completed by the company up to 27.08.2012 (study list of the company)
- Results of a search in bibliographical databases and trial registries for studies on saxagliptin (last search 03.09.2012 in bibliographical databases, and 27.08.2012 in trial registries, searches by the company)
- Results of a search in bibliographical databases for further studies (systematic reviews on cardio- and cerebrovascular outcomes for the drugs to be assessed and the ACT, last search 07.09.2012 in bibliographical databases, searches by the company)

Further information on the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 3A, Sections 3.1.2 and 3.1.3 of the dossier and in Module 4A, Sections 4.2.2 and 4.2.3 of the dossier, and in sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

Combination of saxagliptin and metformin

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

- Studies on metformin plus saxagliptin completed by the company up to 27.08.2012 (study list of the company)
- Results of a search in bibliographical databases and trial registries for studies on saxagliptin (last search 03.09.2012 in bibliographical databases, and 27.08.2012 in trial registries, searches by the company)

Further information on the inclusion criteria for studies in the present 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 Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

No relevant studies for either therapeutic indication were identified in the steps of information retrieval mentioned. The data submitted by the company were unsuitable for assessing the added benefit of the combination of saxagliptin plus metformin in comparison with the respective ACT mentioned above. This is justified below.

Combination of saxagliptin and metformin

The company cited 3 studies for the therapeutic indication “saxagliptin plus metformin” in comparison with sulfonylureas plus metformin. They include 2 placebo-controlled studies, which the company did not use for deriving conclusions on the added benefit however.

The company did not submit any direct comparative studies on the combination of saxagliptin and metformin versus the ACT specified by the G-BA (metformin and sulfonylurea [glibenclamide or glimepiride]). The only study the company included in the assessment was D1680C00001, which compared the (free) combination of saxagliptin plus metformin with glipizide plus metformin. The company named the equivalence of glipizide with glimepiride or glibenclamide as a key argument for including this study. To prove the equivalence, the company conducted a search in bibliographical databases for RCTs that compared glipizide with glimepiride or glibenclamide. The company summarized the 5 studies identified – all of them on the comparison of glipizide with glibenclamide – [4-8] in a meta-analysis, but data were available for only a few of the outcomes considered by the company, and not for all of the 5 studies, either. Because from the company's point of view, there was no statistically significant difference between glipizide and glibenclamide regarding efficacy and safety, the company considered the equivalence as confirmed.

The basic approach of the company to search for relevant studies to prove the equivalence of glipizide with glimepiride or glibenclamide is comprehensible. But the company's search for these studies was already incomplete due to limitation of the search period to the years 1991 to 2011. The Institute's orientation search for the period before 1991 and for the year 2012 found 2 additional studies – also exclusively on the comparison of glipizide with glibenclamide [9,10]. Moreover, 3 of the 5 studies identified by the company were too short (< 24 weeks) to prove the equivalence of the sulfonylureas [4-6]. The equivalence of glipizide with glibenclamide or glimepiride could not be proven on the basis of the remaining 4 studies (nor on the basis of the 5 studies originally included by the company). Further information on this and on other arguments put forward by the company on the relevance of the study D1680C00001 can be found in Section 2.7.1 of the full dossier assessment.

Other investigations

The company included a meta-analysis on saxagliptin (as monotherapy or combination therapy with other oral antidiabetics) as an additional investigation [11] with the goal of assessing the occurrence of cardiovascular events under saxagliptin therapy. The company also cited an – according to the company – indirect comparison of this meta-analysis with 2 further systematic reviews [12,13] with sulfonylureas (alone or in combination with metformin). It used other blood-glucose-lowering therapies as a "common intermediate comparator". This approach of the company was unsuitable for proving an added benefit of saxagliptin plus metformin versus the ACT. Further information can be found in Section 2.7.2.7 of the full dossier assessment.

Combination of saxagliptin and metformin in combination with insulin

The company submitted a direct comparative study (CV181057) for the therapeutic indication "saxagliptin plus metformin in combination with insulin". This study was not suitable for assessing the added benefit, as in the study it was mostly prohibited to adapt the insulin therapy to individual necessities in the comparator group.

Study CV181057 included patients who had received previous therapy with insulin (plus metformin if necessary) that had been inadequate. In the beginning of the study, the patients went through a 4-week run-in phase with diet and exercise. The basic therapy that had been started before (insulin, plus metformin if necessary) was to be continued unchanged during the run-in phase. The run-in phase was followed by the treatment phase, which consisted of 2 phases ("stable insulin phase", 24 weeks, and "flexible insulin phase", 28 weeks).

In the stable insulin phase, the basic therapy (insulin, plus metformin if necessary) was still to remain unchanged, i.e., neither the type of insulin nor the kind of insulin therapy (e.g. basal-supported oral therapy) was permitted to be changed. Changing to a flexible therapy was only allowed when the criteria for emergency treatment were met. Moreover, possible adjustments of the insulin dose had to be discussed with the investigator, who was, however, to encourage the patients to maintain their insulin dose.

The patients' therapy from the first treatment phase was continued in the flexible insulin phase (no new randomization). But in contrast to the first treatment phase, the insulin dosage and the type of insulin administered could be changed individually in both treatment arms. However, it was unclear according to which criteria a change to a different type of insulin was performed, and whether changing the type of insulin and, if necessary, the insulin regimen, was accompanied by an adequate patient education course. Moreover, because at this point the patients in the intervention arm had already been treated with saxagliptin for 24 weeks, while the patients in the comparator arm had received no optimization of their previous treatment, the intervention and control group no longer had the same conditions when the second treatment phase started. Overall, as with the first treatment phase, the results of the second treatment phase and thus the entire study CV181057 could not be used for assessing the added benefit.

Further information on the design of study CV181057 can be found in Section 2.7.2.3.2 of the full dossier assessment.

Summary

In summary, there were no relevant studies for either therapeutic indication for assessing the added benefit of the combination of saxagliptin plus metformin. This deviates from the company's approach, which performed a direct comparison with one study for each of the two therapeutic indications, and submitted further investigations for the therapeutic indication "saxagliptin plus metformin".

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A and 4B, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.4 Results on added benefit

Combination of saxagliptin and metformin

There were no relevant studies for the therapeutic indication "saxagliptin plus metformin". Hence for this therapeutic indication there is no proof of an added benefit versus the ACT specified by the G-BA.

This deviates from the company's result, which derived an added benefit from the data it submitted. Moreover, the company determined an added benefit versus DPP-4 inhibitors plus metformin for patients who cannot be treated with sulfonylurea or for whom sulfonylurea is unsuitable, but insulin therapy is not yet indicated.

Combination of saxagliptin und metformin in combination with insulin

There were no relevant studies for the therapeutic indication "saxagliptin plus metformin in combination with insulin". Hence for this therapeutic indication there is no proof of an added benefit versus the ACT specified by the G-BA.

This deviates from the company's result, which derived an added benefit from the data it submitted.

Further information on the results on added benefit can be found in Module 4A and 4B, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of added benefit

Combination of saxagliptin and metformin

On the basis of the available data, there is no proof of an added benefit of the combination of saxagliptin and metformin versus the ACT specified by the G-BA. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's assessment, which derived an indication of a considerable added benefit of the combination of saxagliptin and metformin. In addition, it also derived a considerable added benefit for the patient population, defined by the company, that cannot be treated with sulfonylurea or for whom sulfonylurea is unsuitable, but insulin therapy is not yet indicated. There is no information on probability for this population.

Combination of saxagliptin and metformin in combination with insulin

On the basis of the available data, there is no proof of an added benefit of the combination of saxagliptin and metformin in combination with insulin versus the ACT specified by the G-BA. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's assessment, which derived an indication of a minor added benefit of the combination of saxagliptin and metformin in combination with insulin.

The decision regarding added benefit is made by the G-BA.

Further information on the extent and probability of added benefit can be found in Module 4A and 4B, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

Not applicable because the company did not submit any study data in its dossier from which an added benefit of the combination of saxagliptin and metformin or the combination of saxagliptin and metformin in combination with insulin versus the ACT specified by the G-BA can be derived.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/a12-16-saxagliptin-metformin-wirkstoffkombination.986.html?tid=2714.