IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A13-12

Saxagliptin/metformin (new therapeutic indication) – 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 (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 27 June 2013). 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:

Saxagliptin/metformin (new therapeutic indication) – Benefit assessment according to § 35a Social Code Book V

Contracting agency:

Federal Joint Committee

Commission awarded on:

19 March 2013

Internal Commission No.:

A13-12

Address of publisher:

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

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

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
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)
IR	immediate release
RCT	randomized controlled trial
SGB	*Sozialgesetzbuch* (Social Code Book)
SPC	Summary of Product Characteristics
XR	extended release

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 a therapeutic indication for the fixed combination of saxagliptin and metformin (hereinafter referred to as "saxagliptin/metformin") newly approved in February 2013. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to “the company”). The dossier was sent to IQWiG on 19 March 2013.

Research question

The benefit assessment was conducted for the new therapeutic indication of saxagliptin/metformin (wording in the Summary of Product Characteristics [SPC]):

- in combination with a sulfonylurea (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 the maximally tolerated dose of both metformin and the sulfonylurea does not provide adequate glycaemic control.

For this new therapeutic indication, the company only requested consultation on the appropriate comparator therapy (ACT) for the individual substance saxagliptin, but not for saxagliptin/metformin. The G-BA specified the following ACT for the individual substance saxagliptin:

- Metformin + human insulin (note: treatment only with human insulin if metformin is not sufficiently effective)

The company concurred with this ACT specified by the G-BA also for saxagliptin/metformin.

The benefit assessment for the therapeutic indication of saxagliptin/metformin plus sulfonylurea was conducted in comparison with the ACT specified by the G-BA. The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs) (minimum duration ≥ 24 weeks).

Results

No relevant study for the assessment of the added benefit of saxagliptin/metformin plus sulfonylurea versus the ACT was identified.

In contrast, the company conducted an adjusted indirect comparison of saxagliptin/metformin plus sulfonylurea versus the ACT.

On the saxagliptin side, the company included a placebo-controlled study (D1680L00006). This study investigated the comparison of saxagliptin plus metformin plus sulfonylurea versus

placebo plus metformin plus sulfonylurea. The company chose metformin plus sulfonylurea (plus placebo) as intermediate comparator. In principle, this study was suitable for an indirect comparison versus the ACT. However, a large proportion of the patients was treated with gliclazide instead of glibenclamide (as in 2 of the studies with the ACT), without this being addressed by the company.

On the comparator side, the company included 3 studies, which were relevant from the company's point of view. In all 3 studies, an inappropriate patient population was studied (no patients with inadequate glycaemic control under a maximum tolerated dose of both metformin and sulfonylurea). They were also too short (study duration of < 24 weeks). Optimization of the insulin therapy was not possible or only possible to a limited extent. Moreover, the following reasons were against the usability of the 3 studies:

- Calle-Pascuale 1995 was a non-RCT, in which metformin was only used in a sub-maximum dose (850 mg a day).
- In Kavapil 2006, the sulfonylurea was neither used according to its approval nor in the same way as in the saxagliptin study. In addition, the majority of patients were treated with a metformin dose of less than 1700 mg a day.
- In Malone 2003 also, the sulfonylurea was neither used according to its approval nor in the same way as in the saxagliptin study. It remained unclear how many patients received at least 1700 mg of metformin a day.

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

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 saxagliptin/metformin plus sulfonylurea compared with the ACT is assessed as follows:

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

[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 1-3 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].

The G-BA decides on added benefit.

2.2 Research question

The benefit assessment of saxagliptin/metformin was conducted for a therapeutic indication newly approved in February 2013 (wording in the SPC [3]):

- in combination with a sulfonylurea (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 the maximally tolerated dose of both metformin and the sulfonylurea does not provide adequate glycaemic control.

For this new therapeutic indication, the company only requested consultation on the ACT for the individual substance saxagliptin, but not for saxagliptin/metformin. The G-BA specified the following ACT for the individual substance saxagliptin in combination with metformin + sulfonylurea:

- Metformin + human insulin (note: treatment only with human insulin if metformin is not sufficiently effective)

The company concurred with this ACT specified by the G-BA also for saxagliptin/metformin plus sulfonylurea.

For the relevant therapeutic indication, the company additionally cited a combination therapy consisting of metformin and sulfonylurea plus another dipeptidyl peptidase 4 (DPP-4) inhibitor as alternative comparator therapy. The reason given by the company for its choice of population was that there are therapeutic situations in practice in which the treating doctor does not yet decide to initiate treatment with insulin/human insulin. The company did not describe these therapeutic situations in more details, and did not delimit them from other therapeutic situations. It was therefore unclear what the characteristics of this population were and how it differed from the one for whom insulin treatment is indicated.

The benefit assessment for the therapeutic indication of saxagliptin/metformin plus sulfonylurea was conducted in comparison with the ACT specified by the G-BA. The alternative comparator therapy cited by the company was not considered in the benefit assessment.

The assessment was conducted based on patient-relevant outcomes and on RCTs. Only studies with a minimum duration of 24 weeks were included.

Further information about the research question can be found in Module 3A, Section 3.1 and Module 4A, 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

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 sulfonylurea (studies completed up to 21 January 2013)
- Searches in bibliographical databases and trial registries for studies on saxagliptin/metformin plus sulfonylurea (last search in bibliographical databases 4 February 2013, and in trial registries 21 January 2013)
- Searches in bibliographical databases and trial registries for studies on insulin (with or without metformin) (last search in bibliographical databases 24 January 2013, and in trial registries 12 February 2013)

The Institute's own search:

- Search in bibliographical databases and in trial registries for studies on gliptins to check the search results of the company (last search in bibliographical databases 19 March 2013, and in trial registries 21 March 2013)

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 Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

No relevant study suitable for assessing the added benefit of saxagliptin/metformin plus sulfonylurea versus the ACT was identified from the steps of information retrieval mentioned. The company therefore conducted an indirect comparison. The studies used by the company are described below and reasons are given why they were unsuitable for answering the present research question.

The company conducted an adjusted indirect comparison of saxagliptin/metformin plus sulfonylurea versus metformin plus insulin or versus insulin monotherapy. The company presented 4 studies for this adjusted indirect comparison. On the saxagliptin side, the company included the placebo-controlled study D1680L00006. The company chose metformin plus sulfonylurea (plus placebo) as intermediate comparator. On the comparator side, the company identified 3 studies, which were relevant for an indirect comparison from the company's point of view (Calle-Pascuale 1995 [4], Kavapil 2006 [5] and Malone 2003 [6]). However, all 3 studies were unsuitable for answering the present research question. Table 2 shows the characteristics of the studies and Table 3 a description of the interventions. Table 4 summarizes the reasons for exclusion.

Table 2: Characteristics of the studies included by the company – indirect comparison: saxagliptin/metformin plus sulfonylurea vs. human insulin plus metformin

Study	Study design	Study duration	Population	
			Type of prior treatment	**Criteria for inadequate glycaemic control**
D1680L00006	RCT, double-blind[a], parallel, multicentre	▪ Screening phase: 2 weeks ▪ Treatment: 24 weeks	Prior treatment with a combination of metformin (XR or IR) (≥ 1500 mg) and sulfonylurea (≥ 50% of the maximum recommended dosage), both in maximum tolerated dose for at least 8 weeks before the first study visit	HbA1c ≥ 7% and ≤ 10% on first study visit
Calle-Pascuale 1995	Non-RCT, open-label, parallel	4 months	Prior treatment with sulfonylurea for at least 1 year, and at maximum dose (glipizide 20 mg or equivalent) for the last 6 months at least, without further interventions	HbA1c: more than 2 values > 7% in the last 6 months
Kavapil 2006	RCT, open-label, parallel, multicentre	16 weeks	Prior treatment with metformin monotherapy ≥ 850 mg/day, at least 1 month	"Not adequately controlled" (no information on HbA1c value)
Malone 2003	RCT, open-label, parallel, multicentre	▪ Run-in: 2 weeks ▪ Treatment: 16 weeks	Prior treatment with metformin or a second-generation sulfonylurea for at least 3 months and in maximum clinically effective dose within the last 30 days	HbA1c > 125% of the normal value

a: Applies to saxagliptin and placebo (open-label for sulfonylurea and metformin).
IR: immediate release; RCT: randomized controlled trial; vs.: versus; XR: extended release

Table 3: Characteristics of the interventions in the studies included by the company – indirect comparison: saxagliptin/metformin plus sulfonylurea vs. human insulin plus metformin

Study	Intervention Number of patients	Comparator Number of patients
D1680L00006	▪ Saxagliptin: 5 mg a day ▪ Metformin: continuation of the stable dose given at the start of the study (≥ 1500 mg) ▪ Sulfonylurea[a]: continuation of the stable dose given at the start of the study (≥ 50% of the maximum recommended dosage) ▪ n = 90[b]	▪ Placebo for saxagliptin ▪ Metformin: continuation of the stable dose given at the start of the study (≥ 1500 mg) ▪ Sulfonylurea[a]: continuation of the stable dose given at the start of the study (≥ 50% of the maximum recommended dosage) ▪ n = 90[b]
Calle-Pascuale 1995[c]	▪ Zn-insulin: 0.3 IU/kg once a day ▪ N = 12	▪ Sulfonylurea: no information about the sulfonylurea used ▪ Metformin: 850 mg once a day ▪ N = 12
Kavapil 2006[c]	▪ BIAsp 30: initial dose 0.2 IU/kg a day (distributed to twice a day), individual up-titration every 1 – 7 days in steps of 2 – 4 units/injection ▪ Metformin: mean dose (range) approximately 1660 mg (500 – 3000 mg)[e] a day ▪ N = 116	▪ Glibenclamide: initial dose 1.75 mg once a day up to 10.5 mg maximum[d] ▪ Metformin: mean dose (range) approximately 1660 mg (500 – 3000 mg)[e] a day ▪ N = 114
Malone 2003	▪ Insulin lispro mix (25% insulin lispro and 75% NPL): dosage depending on target blood glucose level: < 7 mmol/l, 2 hours after a meal < 10 mmol/l without increasing the frequency of hypoglycaemia ▪ Metformin: 1500 – 2550 mg[e] (distributed to 2 – 3 times a day), stable dose after third visit[g] ▪ N = 296	▪ Glibenclamide: dosage depending on target blood glucose level: < 7 mmol/l[f] ▪ Metformin: 1500 – 2550 mg[e] (distributed to 2 – 3 times a day), stable dose after third visit[g] ▪ N = 301

a: Sulfonylureas used: glibenclamide (7.8%), gliclazide (42.4%), glimepiride (46.3%), glipizide (3.5%). Percentages (Institute's calculations) refer to the total population. No information was available for the relevant target population.
b: Relevant target population who received ≥ 1700 mg metformin.
c: Third comparator group not relevant/not used by the company.
d: Maximum dose could be exceeded; administration was then distributed to twice a day; no information on the doses and on the proportion of patients taking > 10.5 mg.
e: No information on the proportion of patients with adequate metformin dosage.
f: Average dosage 14.2 mg (not approval-compliant; approval: 10.5 mg/day maximum); no information on the proportion of patients who received a dose of > 10.5 mg.
g: Mean dose (no information on variance): intervention: 1813 mg, intermediate comparator: 1968 mg; no information on the proportion of patients with adequate metformin dosage.
BIAsp 30: biphasic insulin aspart 30; IU: international units; N: number of randomized patients; n: relevant target population; NPL: neutral protamine lispro; RCT: randomized controlled trial; vs.: versus; Zn: zinc intermediate acting

Table 4: Overview of the reasons for exclusion of the studies – indirect comparison: saxagliptin/metformin plus sulfonylurea vs. human insulin plus metformin

	Reasons for exclusion				
Comparison Study	**Study design**	**Population (type of prior treatment)**	**Study duration**	**Interventions/ACT**	**Intermediate comparators**
Saxagliptin/metformin + sulfonylurea vs. placebo + metformin + sulfonylurea					
D1680L00006				○	○
Insulin vs. sulfonylurea plus metformin					
Calle-Pascuale 1995	●	●	●	●	●
Insulin plus metformin vs. sulfonylurea plus metformin					
Kavapil 2006		●	●	●	●
Malone 2003		●	●	●	●

●: reason for exclusion; ○: uncertainty
ACT: appropriate comparator therapy; vs.: versus

In principle, the placebo-controlled study D1680L00006 concurred with the inclusion and exclusion criteria of the present research question. The relevant target population for the present therapeutic indication had to have received at least 1700 mg of metformin a day. For the study D1680L00006, results were available for this population. Hence the study, in principle, was suitable for an indirect comparison versus the ACT using the intermediate comparator "metformin plus sulfonylurea plus placebo", but there was uncertainty regarding the sulfonylureas used. A large proportion (42.4%) of the patients enrolled in the study were treated with gliclazide instead of glibenclamide (as in 2 of the other studies with the ACT). So it remained unclear whether the comparator intervention would be suitable as intermediate comparator for the indirect comparison with the other studies. The company did not address this issue. It should also be noted that the patients enrolled in the study were treated both with metformin extended release (XR) and with metformin immediate release (IR). The metformin XR formulation is not approved in Europe [7]. It remained unclear how many patients of the relevant target population (daily dose of metformin ≥ 1700 mg) were treated with a metformin XR formulation.

All 3 studies the company used for the comparator side (Calle-Pascuale 1995 [4], Kavapil 2006 [5] and Malone 2003 [6]) were not relevant for the present research question. In all 3 studies, an inappropriate patient population was studied (no patients with inadequate glycaemic control under a maximum tolerated dose of both metformin and sulfonylurea). They were also too short (study duration of < 24 weeks). Optimization of the insulin therapy

was not possible or only possible to a limited extent. Moreover, the following reasons were against the usability of the 3 studies:

- Calle-Pascuale 1995 was a non-RCT. Metformin was only used in a sub-maximum dose (850 mg a day). Moreover, there was no information about which sulfonylurea was used.
- In Kavapil 2006, the sulfonylurea was not used continuously in the maximum tolerated dose, but up-titrated in the course of the study. Hence the type of sulfonylurea treatment concurred neither with the approval requirement nor with the treatment in study D1680L00006. In addition, the maximum dose of glibenclamide of 10.5 mg a day [8] could be exceeded. It remained unclear how large the proportion of patients with approval-compliant dosage was. With a mean total daily dose of metformin of 1660 mg and a range of 500 to 3000 mg, the majority of the patients were treated with a metformin dose of less than 1700 mg.
- The comparator arm in Malone 2003 was also unsuitable as intermediate comparator because the sulfonylurea was not administered continuously in the maximum tolerated dose, but up-titrated. The maximum approved dose of glibenclamide could also be exceeded in Malone 2003. With a metformin dose range of 1500 to 2550 mg a day, it remained unclear how many patients received at least 1700 mg of metformin a day.

Summary

Overall, no relevant data were available for assessing the added benefit of the combination of saxagliptin/metformin plus sulfonylurea versus the ACT, neither for a direct comparison nor for an indirect comparison.

2.4 Results on added benefit

No relevant studies were available for the therapeutic indication to be assessed, neither for a direct comparison, nor for an indirect comparison. Hence the added benefit of saxagliptin/metformin versus the ACT is not proven.

2.5 Extent and probability of added benefit

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

This assessment deviated from that of the company, which did not draw a conclusion on added benefit for saxagliptin/metformin plus sulfonylurea versus the ACT (metformin + human insulin) used by the company. Instead, it derived a hint of a minor added benefit versus insulin monotherapy, which was not defined as ACT by the company (see also Section 2.7.1 and 2.7.2.8.2 of the full dossier assessment).

The G-BA decides on added benefit.

2.6 List of included studies

Not applicable as the studies included by the company were unsuitable for conducting an indirect comparison for the relevant therapeutic indication versus the ACT for the reasons stated above.

References for English extract

Please see full dossier assessment for full reference list.

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