IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A13-32

Saxagliptin (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 (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 28 November 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.

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The dossier assessment was prepared under consideration of external medical and scientific expertise. For this assessment, IQWiG used information that it had recently received in the framework of the assessment of the established drug market of gliptins (including saxagliptin in combination with other antidiabetics) (commissions A13-01, A13-02, A13-03, A13-16 and A13-17). The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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[2] Due to legal data protection regulations, employees have the right not to be named.

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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)
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 a therapeutic indication newly approved in July 2013 of the drug saxagliptin. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 22 August 2013.

Research question

The aim of this report is to assess the added benefit of saxagliptin in comparison with the appropriate comparator therapy (ACT) for the treatment of adult patients aged 18 years and older with type 2 diabetes mellitus for the therapeutic indication of the monotherapy that was newly approved in July 2013:

- as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance

The G-BA specified the following ACT:

- sulfonylurea (glibenclamide or glimepiride)

In principle, the company concurred with the G-BA's ACT, but additionally included the sulfonylurea glipizide in its literature search. However, because the company did not present any studies with glipizide, this deviation is without implication.

The benefit assessment of saxagliptin 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

The data presented by the company were unsuitable to draw conclusions on the added benefit of saxagliptin monotherapy.

The company did not present any direct comparative study on saxagliptin versus the ACT (sulfonylurea [glibenclamide or glimepiride]). However, it did conduct a simple adjusted indirect comparison of saxagliptin versus sulfonylurea. The company chose placebo as common comparator.

For saxagliptin, the company included 4 studies that compared saxagliptin with placebo (CV181011, CV181038, D1680C00005 and D1680C00008). For sulfonylurea, it also in-

cluded 4 studies (Garber 2002, Hoffmann 1994, HOE 490 8-USA-202-DM and Segal 1997). In these studies, glibenclamide or glimepiride was compared with placebo.

However, all 8 studies included by the company were unsuitable for answering the present research question. None of the 8 studies investigated the patient population of interest – patients with contraindication or intolerance to metformin. In addition, some studies were unsuitable for the assessment because the study duration was too short or the sulfonylurea was not administered in compliance with its approval.

Overall, no relevant data were available for assessing the added benefit of the monotherapy with saxagliptin versus the ACT (sulfonylurea [glibenclamide or glimepiride]), neither for a direct, 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 the drug saxagliptin compared with the ACT is assessed as follows:

No proof of added benefit of saxagliptin versus the ACT specified by the G-BA could be derived from the data presented. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of this report is to assess the added benefit of saxagliptin in comparison with the ACT for the treatment of adult patients aged 18 years and older with type 2 diabetes mellitus for the therapeutic indication of the monotherapy that was newly approved in July 2013 [3]:

- as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance

The G-BA specified the following ACT:

- sulfonylurea (glibenclamide or glimepiride)

In principle, the company concurred with the ACT specified by the G-BA. However, apart from the 2 sulfonylureas specified by the G-BA, the company also included glipizide in its literature search, and did not consider the limitation to the sulfonylureas glibenclamide and glimepiride. According to the commission by the G-BA, direct comparative studies versus glipizide would be assessed in a separate research question. However, the company did not present any direct comparative studies versus glipizide and also included only studies with glibenclamide or glimepiride in its indirect comparison.

Moreover, the company defined from its point of view an additional patient group in whom sulfonylureas cannot be used, and in whom insulin is not yet indicated. It specified dipeptidyl peptidase 4 (DPP-4) inhibitors as alternative comparator therapy for these patients. It did not provide clear characteristics of this patient population. Furthermore, the company did not follow this population any further in the research question or in the choice of studies and did not present any data for this population.

The benefit assessment of saxagliptin was conducted in summary in comparison with the ACT specified by the G-BA. The alternative comparator therapy specified 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 3, 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 (studies completed up to 5 July 2013)
- bibliographical literature search on saxagliptin (last search on 9 July 2013)
- search in trial registries for studies on saxagliptin (last search on 15 July 2013)
- bibliographical literature search on sulfonylureas (last search on 12 July 2013)
- search in trial registries for studies on sulfonylureas (last search on 15 July 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

The data presented by the company were unsuitable to draw conclusions on the added benefit of saxagliptin monotherapy. This is justified below.

Direct comparisons

The company did not present any direct comparative study on saxagliptin versus the ACT (sulfonylurea [glibenclamide or glimepiride]).

Indirect comparisons

The company presented a simple adjusted indirect comparison of saxagliptin versus sulfonylurea. The company chose placebo as common comparator. For saxagliptin, the company included 4 studies that compared saxagliptin with placebo. For sulfonylurea, it also included 4 studies. In these studies, glibenclamide or glimepiride was compared with placebo.

However, all 8 studies included by the company were unsuitable for answering the present research question. Table 2 shows an overview of the reasons for exclusion.

Table 2: Overview of the reasons for exclusion of the studies – indirect comparison: saxagliptin vs. sulfonylurea (glimepiride or glibenclamide)

Study	Reasons for exclusion			
	Population	Study duration	Approved maximum dose of sulfonylurea exceeded	Titration of sulfonylurea lacking or not compliant with approval
Saxagliptin vs. placebo				
CV181011	●			
CV181038	●			
D1680C00005	●			
D1680C00008	●			
Sulfonylurea (glimepiride or glibenclamide) vs. placebo				
Garber 2002	●	●		
Hoffmann 1994	●			●
HOE 490 8-USA-202-DM (Schade 1998)[a]	●	●	●	
Segal 1997	●			●
a: HOE 490 8-USA-202-DM was the same study as Schade 1998 in the assessment of sitagliptin (Commission A13-02).				

None of the 8 studies investigated the patient population of interest – patients with contraindication or intolerance to metformin. Some of the studies were also unsuitable for the assessment because they were too short (Garber 2002 [4] and HOE 490 8-USA-202-DM [5,6]), or because the sulfonylurea was not used in compliance with its approval (Hoffmann 1994 [7], HOE 490 8-USA-202-DM [5,6] and Segal 1997 [8]).

A comprehensive presentation of the studies of the indirect comparison and the reasons for exclusion can be found in Appendix A of the full dossier assessment. Additionally, it should be noted that all 4 sulfonylurea studies were also used in the dossier on the drug sitagliptin (different company) and were also excluded from the assessment with justification (Commission A13-02 [9]).

Summary

Overall, no relevant data were available for assessing the added benefit of the monotherapy with saxagliptin versus the ACT (sulfonylurea [glibenclamide or glimepiride]), neither for a direct, nor for an indirect comparison.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.7.2.3.1 and 2.7.2.3.2 and in Appendix A of the full dossier assessment.

2.4 Results on added benefit

No relevant data 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 versus the ACT is not proven.

2.5 Extent and probability of added benefit

No proof of added benefit of saxagliptin versus the ACT specified by the G-BA could be derived from the data presented. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

This assessment deviates from that of the company, which derived an indication of a minor added benefit of saxagliptin versus the ACT. In addition, the company did not derive an added benefit versus the "alternative comparator therapy" (DPP-4 inhibitors) defined by the company itself.

The G-BA decides on the added benefit.

2.6 List of included studies

The information usually provided here is 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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