



IQWiG Reports – Commission No. A18-65

**Sitagliptin
(type 2 diabetes mellitus) –**

**Benefit assessment according to §35a
Social Code Book V¹
(expiry of the decision)**

Extract

¹ Translation of the executive summary of the dossier assessment *Sitagliptin (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 19 December 2018). Please note: This document was translated by an external translator and 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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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 drug sitagliptin. For the drug to be assessed, the pharmaceutical company (hereinafter referred to as the “company”) submitted a dossier for early benefit assessment for the first time as per 27 March 2013. It was assessed in dossier assessment A13-02. The G-BA limited the validity period of this decision. By 1 July 2016, after expiry of the decision, the company submitted a dossier for another benefit assessment of sitagliptin. It was assessed in benefit assessment A16-44. The validity period of the resulting decision was again limited by the G-BA since informative data for the assessment of sitagliptin-induced diabetic late complications, such as retinopathy, hypoglycaemia, and hospitalization due to hyperglycaemia, are still missing. After expiry, the company submitted another dossier, which was sent to IQWiG on 28 September 2018. The assessment is based on the dossier compiled by the company.

Research question

This aim of this report is to assess the added benefit of sitagliptin as oral dual combination therapy with metformin in comparison with the appropriate comparator therapy (ACT) for the treatment of adult patients with type 2 diabetes mellitus if diet and exercise plus metformin monotherapy did not provide adequate glycaemic control.

For the relevant research question, the G-BA specified the ACT presented in Table 2. For easier traceability, the research question investigated in this report is referred to as research question B to match its designation in the first and second assessment of sitagliptin.

Table 2²: Research questions of the benefit assessment of sitagliptin plus metformin

Research question	Indication	ACT ^a
B	Sitagliptin plus metformin	<ul style="list-style-type: none"> ▪ Sulfonylurea (glibenclamide or glimepiride)^b plus metformin or ▪ Empagliflozin plus metformin or ▪ Liraglutide^c plus metformin
<p>a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in bold.</p> <p>b: As commissioned by the G-BA, studies with direct comparisons versus glipizide are to be additionally assessed.</p> <p>c: Liraglutide in combination with further medications for the treatment of cardiovascular risk factors, particularly antihypertensives, anticoagulants, and/or lipid-lowering drugs and only for patients with manifest cardiovascular disease [1].</p> <p>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee</p>		

² Table numbers start with “2” as numbering follows that 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, which corresponds to the company's inclusion criteria, were used for deriving any added benefit.

Results

Research question B: Combination of sitagliptin plus metformin

In this assessment, the added benefit of sitagliptin plus metformin is assessed – in 2 separate research questions – in comparison with the ACT of sulfonylureas (glibenclamide, glimepiride) plus metformin (research question B1) and additionally in comparison with glipizide plus metformin (research question B2).

Research question B1: Sitagliptin plus metformin versus sulfonylurea (glibenclamide, glimepiride) plus metformin

Study pool and study characteristics

For the comparison of sitagliptin plus metformin with sulfonylurea (glibenclamide, glimepiride), 2 studies were available, each of which comparing sitagliptin plus metformin with glimepiride plus metformin (P803 and HARMONY 3 studies). Both studies have already been presented and assessed in the previous assessment of sitagliptin (see dossier assessment A16-44).

Results

The results of the P803 and HARMONY 3 studies have been presented in detail in the previous assessments of sitagliptin. Overall, there was a statistically significant difference in favour of sitagliptin for non-serious symptomatic hypoglycaemia (blood glucose ≤ 7 mg/dL).

In its dossier, the company presented a new analysis on the outcome of non-severe symptomatic hypoglycaemia from the HARMONY 3 study, using a blood glucose threshold of 50 mg/dL. For this operationalization, a statistically significant difference in favour of sitagliptin was found as well. The newly submitted analysis therefore confirms the result of the previous benefit assessment.

Furthermore, the company submitted new analyses on the outcomes of change in visual acuity (HARMONY 3 study) and diabetic retinopathy (P803 and HARMONY 3). However, these analyses are unsuitable for this benefit assessment.

Research question B2: Sitagliptin plus metformin versus glipizide plus metformin

Study pool and study characteristics

Like in the previous assessments, 1 study, which compared sitagliptin plus metformin with glipizide plus metformin (P024 study), was available for this research question. This study has already been presented and assessed in the prior assessments of sitagliptin (see dossier assessments A13-02 and A16-44).

Results

The results on added benefit have been presented in detail in the first and second assessments of sitagliptin. For each of the 3 outcomes of all-cause mortality, symptomatic hypoglycaemia (blood glucose ≤ 50 mg/dL), as well as severe hypoglycaemia, there was a statistically significant difference in favour of sitagliptin.

The dossier submitted by the company included new analyses on the outcome of diabetic retinopathy. These analyses are unsuitable for this benefit assessment.

Subgroups

To prove different effects, subgroup analyses are conducted only if each subgroup comprises at least 10 persons or, in case of binary data, if at least 10 events occurred in a subgroup. For this reason, this benefit assessment – unlike in the first and second assessments of sitagliptin plus metformin – presents no subgroup analysis on all-cause mortality by sex. Accordingly, the conclusion on added benefit regarding all-cause mortality is drawn for the total population and not, as previously, restricted to the subgroup of men. This results in a hint of added benefit of sitagliptin in comparison with glipizide for the outcome of all-cause mortality.

TECOS long-term cardiovascular study

For the dossier assessment A16-44, the company presented the TECOS long-term cardiovascular study. For this benefit assessment, the company did not present any new long-term studies. Instead it discussed previously known data on individual outcomes from the TECOS study against the backdrop of the G-BA's reasoning for limiting the validity period of the decision on diabetic late complications. In addition, the company presented new selective subgroup analyses on these outcomes, for instance by region, as well as data on patient characteristics and the course of the study for the subgroup of Western Europe.

Like in the previous assessment of sitagliptin (commission A16-44), the company did not present any analyses of the TECOS study related to research question B. The data newly presented by the company on the TECOS study do not reveal any relevant insights on the TECOS study beyond those already known from the previous assessment of sitagliptin.

Results from the TECOS study

The assessment of the TECOS study in A16-44 showed the following results for the use of sitagliptin in comparison with placebo, each in addition to “standard diabetes treatment”:

- No advantage and no disadvantage of sitagliptin regarding all-cause mortality, as well as cardiovascular morbidity and mortality.
- A disadvantage of sitagliptin for the outcome of retinopathy.
- At the same time, no conclusions can be drawn for the outcomes of symptomatic, confirmed hypoglycaemia as well as severe hypoglycaemia because there were no analyses in a valid operationalization.

There was a statistically significant result in favour of sitagliptin for the outcome of hospitalizations due to hyperglycaemia. This supports the observation that no adequate antihyperglycaemic treatment was provided in the comparator arm because blood glucose imbalances were more common than in the sitagliptin arm.

Further topics discussed by the company

In addition to the above research question, the company reported working on further topics related to diabetic late complications and presented corresponding evidence in the section “Further investigations”. For this purpose, the company conducted information retrievals regarding randomized cardiovascular long-term studies, RCTs for a metaanalysis on the outcome of diabetic retinopathy (in part using individualized patient data [PD]), as well as non-randomized comparative studies. The inclusion and exclusion criteria reported by the company on these information retrievals are not limited to the current research question, however. The identified studies also investigate, for instance, different populations, interventions, and comparator therapies. In addition, some of the studies included by the company have a study duration of fewer than 24 weeks. The company did not state why these data would translate to the research question of this benefit assessment. All things considered, the further investigations presented by the company are therefore unsuitable for this benefit assessment.

Aside from the fact that the investigations presented by the company do not address the research question of the dossier assessment, they are not suitable for confirming or falsifying the results of the TECOS study. The analyses presented by the company do not correspond to the comparisons within the TECOS study (modification of the “standard therapy” with sitagliptin versus placebo), do not investigate the TECOS population (patients with prior cardiovascular diseases), and do not have a long enough treatment duration.

Probability and extent of added benefit

On the basis of the presented results, the probability and extent of added benefit of sitagliptin plus metformin in comparison with sulfonylureas (glimepiride, glibenclamide) or in comparison with glipizide, each in combination with metformin, are assessed as follows:

Research question B1: Probability and extent of added benefit, patient groups with therapeutically important added benefit³

All things considered, as in the previous assessment of sitagliptin, a positive effect remains for non-severe hypoglycaemia.

Regarding mortality and diabetic late complications, the company did not present any relevant new data. As already noted in the A16-44 dossier assessment, for these outcomes, the HARMONY 3 study revealed neither an advantage nor a disadvantage for the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin. However, like the P803 study, the HARMONY 3 study was not designed to investigate these outcomes. Like in the first and second assessment, sufficient data are still not available on these outcomes.

Overall, the result of the prior assessment therefore remains unchanged: For sitagliptin plus metformin in comparison with glimepiride plus metformin, there is a hint of non-quantifiable, at most considerable, added benefit.

Research question B2: Probability and extent of added benefit, patient groups with therapeutically important added benefit

In summary, only positive effects remain in the overall assessment on the outcome level (all-cause mortality, non-severe hypoglycaemia, as well as severe hypoglycaemia).

The company did not present any relevant new data regarding microvascular and macrovascular late complications. As already noted in the dossier assessment in A13-02, for these outcomes, neither an advantage nor a disadvantage was found for the combination of sitagliptin plus metformin in comparison with glipizide plus metformin. However, the P024 study was not designed to investigate these outcomes. Like in the first and second assessment, sufficient data are still not available on these outcomes.

Due to the treat-to-target strategy with a uniform near-normal target, conclusions are limited to patients with a near-normal blood glucose target.

Overall, this results in a hint of considerable added benefit of sitagliptin in comparison with glipizide in combination with metformin. In each case, this added benefit is limited to patients with a near-normal blood glucose target. For patients with a different treatment goal, there is no proof of added benefit of sitagliptin.

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].

Summary

Table 3 presents a summary of the probability and extent of the added benefit of sitagliptin in combination with metformin.

Table 3: Sitagliptin plus metformin – extent and probability of added benefit

Research question	Indication	Comparator therapy ^a	Extent and probability of added benefit
B1	Sitagliptin plus metformin	<ul style="list-style-type: none"> ▪ Sulfonylurea (glibenclamide or glimepiride) plus metformin or ▪ Empagliflozin plus metformin or ▪ Liraglutide^b plus metformin 	Hint of added benefit (extent not quantifiable, at most considerable)
B2	Sitagliptin plus metformin	<ul style="list-style-type: none"> ▪ Glipizide plus metformin^c 	<i>Treatment goal of near-normal blood glucose control:</i> Hint of considerable added benefit <i>Different treatment goal:</i> Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.

b: Liraglutide in combination with further medication for the treatment of the cardiovascular risk factors, particularly antihypertensives, anticoagulants, and/or lipid lowering drugs and only for patients with manifest cardiovascular disease [1].

c: As commissioned by the G-BA, directly comparative studies of sitagliptin plus metformin versus glipizide plus metformin were additionally assessed.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

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.

1. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; 375(4): 311-322.
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The full report (German version) is published under <https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-65-sitagliptin-type-2-diabetes-mellitus-benefit-assessment-according-to-35a-social-code-book-v-expiry-of-the-decision.10626.html>.