IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

## Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Sitagliptin/Metformin – 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.

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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 |
| BfArM | *Bundesinstitut für Arzneimittel und Medizinprodukte* (Federal Institute for Drugs and Medical Devices) |
| CT | conventional insulin treatment |
| G-BA | *Gemeinsamer Bundesausschuss* (Federal Joint Committee) |
| HbA1c | glycosylated haemoglobin A1c |
| ICT | intensified conventional insulin treatment |
| IQWiG | *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care) |
| OAD | oral antidiabetic |
| 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 drugs sitagliptin/metformin. The benefit assessment formed part of the assessment of the established drug market of gliptins, which was commissioned by the G-BA on 7 June 2012. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 27 March 2013.

### Research question and appropriate comparator therapy

The benefit assessment of the fixed combination of sitagliptin and metformin (hereinafter referred to as "sitagliptin/metformin") was conducted in accordance with its approval status for the following therapeutic indication: treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise.

Within this therapeutic indication, different subindications for the use of sitagliptin/metformin and thus different research questions result from the type of prior treatment.

According to the company's consultation request to the G-BA, an appropriate comparator therapy (ACT) was specified for each of the subindications. This benefit assessment concurs with the G-BA's specifications.

Table 2: Subindications and ACT for sitagliptin/metformin

| Research question[a] | Subindication | ACT specified by the G-BA |
|---|---|---|
| A | Sitagliptin/metformin | Sulfonylurea (glibenclamide, glimepiride)[b] plus metformin |
| B | Sitagliptin/metformin plus sulfonylurea | Human insulin plus metformin<br>(Note: treatment only with human insulin if metformin is not sufficiently effective) |
| C | Sitagliptin/metformin plus insulin | Human insulin plus metformin<br>(Note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective) |
| a: Designation corresponds to the coding in the company's dossier.<br>b: According to the commission by the G-BA, direct comparative studies versus glipizide were to be additionally assessed.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics | | |

***Deviations by the company***

In none of the 3 subindications, the company limited the study inclusion to studies with approval-compliant daily dosage of the fixed combination (sitagliptin: 100 mg; metformin: at least 1700 mg).

In the subindication sitagliptin/metformin versus sulfonylurea plus metformin (research question A), the company included studies with sulfonylureas without limitation to the drugs specified by the G-BA (glibenclamide and glimepiride). According to the commission by the G-BA, direct comparative studies versus glipizide were additionally assessed.

In the subindication sitagliptin/metformin plus insulin (research question C), the company cited conventional insulin treatment (CT), intensified conventional insulin treatment (ICT) and insulin dose increase as comparator therapies. This constituted an appropriate specification of the ACT. Different insulin treatment regimens may be medically advisable to optimize the treatment for the individual patient. Studies in which the patients had the possibility to optimize their treatment on an individual basis (including switching treatment type and regimen) were included in this benefit assessment.

**Results**

***Sitagliptin/metformin versus sulfonylurea plus metformin***

The added benefit – in 2 separate research questions – was assessed versus the ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride] plus metformin) (research question A1) and, additionally, versus glipizide plus metformin (research question A2) in this assessment. One study was available for each of the research questions: in the study P803, sitagliptin/metformin was compared with glimepiride plus metformin, and in the study P024, sitagliptin/metformin was compared with glipizide plus metformin. Both studies were not relevant for the assessment of the fixed combination sitagliptin/metformin because it was unclear whether and, if any, how many patients received the metformin dose of at least 1700 mg/day, which concurs with the approval of the fixed combination sitagliptin/metformin. The company did not prove that the results of the studies were independent from the metformin dose administered. The company presented the same studies P803 and P024 for the dossier assessment on sitagliptin (A13-02), which was prepared at the same time. In case of a proof that the results of both studies do not depend on the metformin dose, the results cited in the dossier assessment A13-02 could also be used for the fixed combination sitagliptin/metformin.

In contrast, the company assessed the added benefit of sitagliptin/metformin versus sulfonylureas (without limitation to individual drugs) plus metformin without consideration of the approval-compliant metformin dose, and derived it using a meta-analysis of the 2 studies P803 and P024.

***Sitagliptin/metformin plus sulfonylurea versus human insulin (if applicable plus metformin)***

The company identified no study on sitagliptin/metformin plus sulfonylurea versus the ACT.

***Sitagliptin/metformin plus insulin versus human insulin (if applicable plus metformin)***

In its assessment, the company included the study Hong 2012, in which the additional administration of sitagliptin in comparison with an insulin dose increase on the basis of an ongoing insulin treatment and additional oral antidiabetic treatment was investigated. The study was not relevant for the benefit assessment because fewer than half of the patients treated received metformin. The other oral antidiabetics (OADs) used in the study were α-glucosidase inhibitors, sulfonylureas, glinides and glitazones. Sitagliptin is not approved in combination with these combination partners – with the exception of glitazones, which are not relevant for this assessment, however. There was no analysis for the patients treated according to the approval.

Moreover, it was unclear whether and, if any, how many patients received the metformin dose of at least 1700 mg/day, which concurs with the approval of the fixed combination sitagliptin/metformin.

**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 sitagliptin/metformin compared with the ACT and, additionally, versus glipizide is assessed as follows:

[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].

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

| Research question | Subindication | Comparator therapy | Extent and probability of added benefit |
|---|---|---|---|
| A1 | Sitagliptin/metformin | Sulfonylurea (glibenclamide, glimepiride) plus metformin | Added benefit not proven[b] |
| A2 | Sitagliptin/metformin | Glipizide plus metformin[a] | Added benefit not proven[b] |
| B | Sitagliptin/metformin plus sulfonylurea | Human insulin plus metformin (Note: only human insulin if metformin is not sufficiently effective) | Added benefit not proven |
| C | Sitagliptin/metformin plus insulin | Human insulin plus metformin (Note: only human insulin if metformin is not tolerated according to the SPC or not sufficiently effective) | Added benefit not proven |

a: According to the commission by the G-BA, direct comparative studies versus glipizide were to be additionally assessed.
b: The company presented the same studies P803 and P024 for these research questions in the dossier assessment on sitagliptin (A13-02), which was prepared at the same time. In case of a proof that the results of both studies do not depend on the metformin dose, the assessment on extent and probability of added benefit cited in the dossier assessment A13-02 could also be used for the fixed combination sitagliptin/metformin.
G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

As the added benefit is not proven for any subindication, there are also no patient groups for whom a therapeutically important added benefit could be derived.

The G-BA decides on added benefit.

## 2.2 Research questions

The benefit assessment of the fixed combination of sitagliptin/metformin was conducted according to the Summary of Product Characteristics (SPC) [3] for the treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise in the following subindications:

- **Sitagliptin/metformin** in patients in whom metformin monotherapy in the maximum tolerated dose does not provide adequate glycaemic control or those already being treated with the combination of sitagliptin and metformin.
- **Sitagliptin/metformin in combination with a sulfonylurea** in patients in whom a combination of the maximum tolerated dose of both metformin and a sulfonylurea does not provide adequate glycaemic control.
- **Sitagliptin/metformin in addition to insulin** in patients in whom a stable insulin dose and metformin alone does not provide adequate glycaemic control.

Moreover, sitagliptin/metformin is also approved in combination with glitazones [3]. However, glitazones are excluded from prescription [4]. This subindication was therefore not considered in this benefit assessment.

The G-BA specified an ACT for each of the different subindications. These are shown in Table 4.

Table 4: Subindications and ACT for sitagliptin/metformin

| **Research question**[a] | **Subindication** | **ACT specified by the G-BA** |
|---|---|---|
| A | Sitagliptin/metformin | Sulfonylurea (glibenclamide, glimepiride)[b] plus metformin |
| B | Sitagliptin/metformin plus sulfonylurea | Human insulin plus metformin<br>(Note: treatment only with human insulin if metformin is not sufficiently effective) |
| **C** | Sitagliptin/metformin plus insulin | Human insulin plus metformin<br>(Note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective) |
| a: Designation corresponds to the coding in the company's dossier.<br>b: According to the commission by the G-BA, direct comparative studies versus glipizide were to be additionally assessed.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics | | |

**Research question A: sitagliptin/metformin**

The G-BA specified sulfonylureas (glibenclamide, glimepiride) plus metformin as ACT for this subindication. According to the commission by the G-BA, direct comparative studies versus glipizide were to be additionally assessed. In this benefit assessment, the added benefit of sitagliptin/metformin was therefore assessed versus the following comparator therapies:

- Research question A1: ACT specified by the G-BA (sulfonylureas [glibenclamide; glimepiride] plus metformin)
- Research question A2: glipizide plus metformin

The valid SPC of glibenclamide or glimepiride was used for the question whether these drugs were used according to their approval [5,6]. As glipizide is no longer approved in Germany, the last SPC valid for Germany was requested from the Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte* [BfArM]) and used [7]. This was from the year 2000. The current SPC from Austria [8], where glipizide is still approved, was additionally used to also take into account current knowledge on the approval-compliant use of glipizide.

The benefit assessment of sitagliptin/metformin was conducted according to the SPC [3] for the patient population described above and the approval-compliant daily dosage of the fixed combination (sitagliptin: 100 mg; metformin: at least 1700 mg). This deviated from the company's approach, which did not limit the study inclusion to studies with the dosages mentioned.

Treatment with sulfonylureas (glibenclamide or glimepiride) plus metformin (research question A1) specified by the G-BA, and, according to the commission by the G-BA, additionally glipizide plus metformin (research question A2) were used as ACT. Regarding the ACT, the company claimed to concur with the G-BA's specification. However, the company included studies with sulfonylureas without limitation to the drugs cited by the G-BA, and did not conduct separate assessments of the added benefit versus the G-BA's ACT and glipizide (but versus sulfonylureas as a whole) (see Section 2.7.2.1 of the full dossier assessment).

**Research question B: sitagliptin/metformin plus sulfonylurea versus human insulin plus metformin**

The assessment of the added benefit of sitagliptin/metformin plus sulfonylurea was conducted according to the SPC [3] for the patient population described above and the approval-compliant daily dosage of the fixed combination (sitagliptin: 100 mg; metformin: at least 1700 mg). Treatment with human insulin plus metformin (if applicable, only human insulin if metformin is not sufficiently effective) specified by the G-BA was used as ACT. The company accepted the ACT specified by the G-BA.

**Research question C: sitagliptin/metformin plus insulin**

The benefit assessment of sitagliptin/metformin plus insulin was conducted according to the SPC [3] for the patient population described above and the approval-compliant daily dosage of the fixed combination (sitagliptin: 100 mg; metformin: at least 1700 mg). Treatment with human insulin plus metformin (if applicable, only human insulin if metformin is not tolerated according to the SPC or not sufficiently effective) specified by the G-BA was used as ACT. This deviated from the company's approach, which did not limit the study inclusion to studies with the dosages mentioned. Regarding the ACT, the company cited CT, ICT and insulin dose increase as comparator therapies. This constituted an appropriate specification of the ACT. Different insulin treatment regimens may be medically advisable to optimize the treatment for the individual patient. Studies in which the patients had the possibility to optimize their treatment on an individual basis (including switching treatment type and regimen) were included in this benefit assessment.

**Summary**

In summary, the assessment of sitagliptin/metformin in the different subindications was conducted versus the ACTs specified by the G-BA. For the research question A (sitagliptin/metformin), the added benefit versus glipizide plus metformin (research question

A2) was also assessed. The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs) with a minimum duration of 24 weeks. Only studies with an approval-compliant administration of sitagliptin (100 mg/day) and metformin (at least 1700 mg/day), according to the SPC of the fixed combination, were included. Studies that were conducted with a free combination of sitagliptin and metformin were also considered provided that the sitagliptin and metformin dosages administered in the studies could be represented by the fixed combination.

*Further information about the research question can be found in Modules 3A-C, Sections 3.1, and in Modules 4A-C, Sections 4.2.1, of the dossier, and in Sections 2.7.2, 2.7.3 and 2.7.4 of the full dossier assessment.*

## 2.3 Research question A: sitagliptin/metformin

### 2.3.1 Information retrieval (research question A)

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 sitagliptin/metformin (studies completed up to 1 February 2013)
- Bibliographical literature search on sitagliptin/metformin (last search on 25 February 2013 – cut-off date 1 February 2013)
- Search in trial registries for studies on sitagliptin/metformin (last search on 1 February 2013)

The Institute's own search:

- Bibliographical literature search on gliptins to check the search results of the company (last search on 19 March 2013)
- Search in trial registries for studies on gliptins to check the search results of the company (last search on 21 March 2013)

No additional studies were identified in the Institute's search.

*Further information about the methods of information retrieval can be found in Module 4A, Section 4.2.3 of the dossier, and in Section 2.7.2.4 of the full dossier assessment.*

### 2.3.2 Research question A1: sitagliptin/metformin versus sulfonylurea (glibenclamide, glimepiride) plus metformin

#### 2.3.2.1 Study pool

The data presented by the company were unsuitable to draw conclusions on the added benefit of the fixed combination sitagliptin/metformin. This is justified below.

The company included the study P803 in its benefit assessment. This was a company-sponsored, randomized, double-blind study with a 30-week treatment duration for the comparison of sitagliptin plus metformin with glimepiride plus metformin. It was conducted in adult patients with type 2 diabetes mellitus with inadequate glycaemic control with a metformin dosage of at least 1500 mg/day (defined as glycosylated haemoglobin A1c [HbA1c] value between 6.5% and 9.0%). The study aimed to investigate the efficacy and safety of an add-on therapy with sitagliptin in comparison with glimepiride on the basis of an ongoing metformin administration.

Patients who, according to the inclusion criteria of the study, had received a stable dose of metformin of at least 1500 mg/day for at least 12 weeks before the start of the study, were included in the study. This dosage was to be maintained during the entire study duration. There was no information in the available documents about whether and, if any, how many patients received the metformin dose of at least 1700 mg/day, which concurs with the approval of the fixed combination sitagliptin/metformin. No such information was available for the period before the start of the study or for the period during the study. The company did not address this issue explicitly. From the company's point of view, the daily dosages of the individual drugs in the studies included were comparable with the daily dosage of the fixed combination. It did not present any data on this, however.

The company did not present any evidence to what extent the results of the total population of the study P803 can be applied to the patients who are treated according to the approval (with a metformin dose of at least 1700 mg/day). The data presented by the company were therefore unsuitable to draw conclusions on the added benefit of sitagliptin/metformin versus the ACT. The target population according to approval also includes patients who have already been treated with a combination of sitagliptin and metformin as separate tablets. The company did not cite this patient population in the inclusion criteria. This approach was not justified.

A detailed description of the study is presented in the dossier assessment on sitagliptin (commission A13-02) [9].

*Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A, Section 4.3.1.1 of the dossier, and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.*

#### 2.3.2.2 Results on added benefit

No relevant data were available for the research question A1 "sitagliptin/metformin". Hence the added benefit versus the ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride] plus metformin) is not proven.

#### 2.3.2.3 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of sitagliptin/metformin in comparison with the ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride] plus metformin). Hence there are also no patient

groups for whom a therapeutically important added benefit could be derived. This result deviates from that of the company, which derived a proof of major added benefit versus sulfonylureas by including an additional study in comparison with glipizide.

The company presented the same study P803 for the dossier assessment on sitagliptin (A13-02) [9], which was prepared at the same time. In case of a proof that the results of this study do not depend on the metformin dose, the results cited in the dossier assessment A13-02 could also be used for the fixed combination sitagliptin/metformin.

*Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.9 of the full dossier assessment.*

### 2.3.3 Research question A2: sitagliptin/metformin versus glipizide plus metformin

#### 2.3.3.1 Study pool

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

The company included the study P024 in its benefit assessment. This was a company-sponsored, randomized, double-blind approval study with a 104-week treatment duration for the comparison of sitagliptin plus metformin with glipizide plus metformin. It was conducted in adult patients with type 2 diabetes mellitus with inadequate glycaemic control with a metformin dosage of at least 1500 mg/day (defined as HbA1c value between 6.5% and 10.0 %). The study aimed to investigate the efficacy and safety of an add-on therapy with sitagliptin in comparison with glipizide on the basis of an ongoing metformin administration.

As described above for the study P803 in research question A1, according to the inclusion criteria, the randomized patients had to have received a metformin dose of at least 1500 mg/day, which was to be maintained during the entire study duration. There was no information in the available documents about whether and, if any, how many patients received the approval-compliant metformin dose of at least 1700 mg/day also for the study P024. There was also no evidence to what extent the results of the total population of the study P024 can be applied to the patients treated according to the approval (with a metformin dose of at least 1700 mg/day). The data presented by the company were therefore unsuitable to draw conclusions on the added benefit of sitagliptin/metformin versus the ACT. The target population according to approval also includes patients who have already been treated with a combination of sitagliptin and metformin as separate tablets. The company did not cite this patient population in the inclusion criteria. This approach was not justified.

Further details can be found in the comments on the study P803 (Section 2.3.2) and in the dossier assessment on sitagliptin (commission A13-02) [9].

*Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A, Section 4.3.1.1 of the dossier, and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.*

#### 2.3.3.2 Results on added benefit

No relevant data were available for the research question A2 "sitagliptin/metformin". Hence the added benefit versus the ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride] plus metformin) is not proven.

#### 2.3.3.3 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of sitagliptin/metformin in comparison with glipizide. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result deviates from that of the company, which derived a proof of major added benefit versus sulfonylureas by including an additional study in comparison with glimepiride.

The company presented the same study P024 for the dossier assessment on sitagliptin (A13-02) [9], which was prepared at the same time. In case of a proof that the results of this study do not depend on the metformin dose, the results cited in the dossier assessment A13-02 could also be used for the fixed combination sitagliptin/metformin.

*Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.9 of the full dossier assessment.*

### 2.4 Research question B: sitagliptin/metformin plus sulfonylurea

#### 2.4.1 Information retrieval and study pool

The company did not identify any direct comparative studies or studies for an indirect comparison on sitagliptin/metformin plus sulfonylurea versus the ACT specified by the G-BA. The company did not claim an added benefit for this subindication.

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 sitagliptin/metformin plus sulfonylurea (studies completed up to 1 February 2013)
- Bibliographical literature search on sitagliptin/metformin plus sulfonylurea (last search on 25 February 2013 – cut-off date 1 February 2013)
- Search in trial registries for studies on sitagliptin/metformin plus sulfonylurea (last search on 1 February 2013)
- Bibliographical literature search on human insulin with or without metformin (last search on 26 September 2012)
- Search in trial registries for studies on human insulin with or without metformin (last search on 26 September 2012)

The Institute's own search:

- Bibliographical literature search on gliptins to check the search results of the company (last search on 19 March 2013)
- Search in trial registries for studies on gliptins to check the search results of the company (last search on 21 March 2013)

No additional studies were identified in the Institute's search.

*Further information on the inclusion criteria for studies in this 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.*

### 2.4.2 Results on added benefit

No relevant data were available for the research question "sitagliptin/metformin plus sulfonylurea". Hence the added benefit versus the ACT specified by the G-BA is not proven.

### 2.4.3 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of sitagliptin/metformin in comparison with the ACT specified by the G-BA (human insulin plus metformin, or only human insulin if metformin is not sufficiently effective). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result concurs with that of the company.

## 2.5 Research question C: sitagliptin/metformin plus insulin

### 2.5.1 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 sitagliptin/metformin plus insulin (studies completed up to 1 February 2013)
- Bibliographical literature search on sitagliptin/metformin plus insulin (last search on 25 February 2013 – cut-off date 1 February 2013)
- Search in trial registries for studies on sitagliptin/metformin plus insulin (last search on 1 February 2013)

The Institute's own search:

- Bibliographical literature search on gliptins to check the search results of the company (last search on 19 March 2013)
- Search in trial registries for studies on gliptins to check the search results of the company (last search on 21 March 2013)

No additional studies were identified in the Institute's search.

*Further information about the methods of information retrieval can be found in Module 4C, Section 4.2.3 of the dossier, and in Section 2.7.4.4 of the full dossier assessment.*

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

The company included a direct comparative study in the assessment. Its characteristics are presented in Table 5 and Table 6.

Table 5: Characteristics of the studies included by the company – RCT, direct comparison: sitagliptin/metformin plus insulin vs. human insulin plus metformin

| **Study** | **Study design** | **Study duration** | **Population** | |
|---|---|---|---|---|
| | | | **Type of prior treatment** | **Criteria for inadequate glycaemic control** |
| Hong 2012 | RCT,<br>parallel,<br>active-controlled,<br>monocentre,<br>open-label | Screening phase:<br>4 weeks,<br>Treatment:<br>24 weeks | Insulin treatment for at least 3 months, with a dosage of ≥ 10 units/day for ≥ 4 before enrolment | HbA1c 7.5 – 11% |
| HbA1c: glycosylated haemoglobin A1c; RCT: randomized controlled trial; vs.: versus | | | | |

Table 6: Characteristics of the interventions – RCT, direct comparison: sitagliptin/metformin plus insulin vs. human insulin plus metformin

| **Study** | **Sitagliptin/metformin plus insulin**<br>**Number of patients** | **Human insulin plus metformin**<br>**Number of patients** |
|---|---|---|
| Hong 2012 | Insulin plus sitagliptin (100 mg/day)<br>N = 70<br>The insulin dose remained unchanged. | Intensification of insulin treatment (insulin dose increase)<br>N = 70<br>The patients were instructed to increase their insulin dose by ≥ 10% over the course of the study (at any time and again at the 12-week follow-up) if their HbA1c was not within the target level (≤ 7.0%). The patients could also adjust their insulin dose by 2 units/week based on their blood glucose levels measured.<br>The patients were instructed to use the same formulation of insulin and, if possible, the same treatment regimen throughout the entire study. |

| **Concomitant treatment** | **Sitagliptin plus insulin plus OAD;** (n = 61)<br>Number of patients (%)[b] | **Insulin intensification plus OAD;** (n = 63)<br>Number of patients (%)[b] |
|---|---|---|
| Sulfonylureas | 15 (24.6) | 15 (23.8) |
| Glinides | 8 (13.1) | 10 (15.9) |
| Metformin | 28 (45.9) | 26 (41.3) |
| Patients thereof with a dose of ≥ 1700 mg/day | Unclear | Unclear |
| Glitazones | 4 (6.6) | 2 (3.2) |
| α-glucosidase inhibitors | 19 (31.1) | 27 (42.9) |

a: The dose of oral antihyperglycaemic drugs was not changed during the study. The investigators could decrease a patient's insulin dose according to their clinical judgments only in the event of severe or repeated hypoglycaemic episodes.
b: A patient could receive several concomitant treatments.
HbA1c: glycosylated haemoglobin A1c; N: number of randomized patients; n: number of analysed patients; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus

Hong 2012 was an exploratory, randomized, open-label study with a 24-week treatment period. Patients aged 30 to 70 years who had received insulin treatment for at least 3 months were enrolled. Insulin treatment had to have been administered at a dose of at least 10 units/day and for a minimum of 4 weeks. The patients were additionally treated with different OADs. The study aimed to investigate the efficacy and safety of an additional administration of sitagliptin in comparison with an insulin dose increase on the basis of an ongoing insulin treatment (and additional oral antidiabetic treatment).

The study Hong 2012 was unsuitable for assessing the added benefit because the patients enrolled did not correspond to the target population. According to Table 1 (demographic data at the start of the study) of the publication [10], only 45.9% of the patients treated in the sitagliptin/metformin plus insulin arm and 41.3% of the patients treated in the human insulin

plus metformin arm received metformin. The other OADs used in the study were α-glucosidase inhibitors, sulfonylureas, glinides and glitazones. Sitagliptin/metformin within an insulin treatment is not approved in combination with these combination partners, however. It was also unclear whether the patients who received metformin were treated with this OAD alone or in combination with one of the other antidiabetic drugs mentioned.

Moreover, only the subpopulation of the patients who received at least 1700 mg/day of metformin (according to the requirements of the SPC of the fixed combination [3]) was relevant for this benefit assessment. The company did not draw conclusions on this target population. There were also no corresponding data in the publication on Hong 2012 [10].

The company used the results of the total population for the assessment of the added benefit of sitagliptin/metformin plus insulin. The company justified this with the fact that the publication did not report subgroup effects. Moreover, the company pointed out that the proportions of patients with and without metformin (44% versus 56% of the total population) were comparable. Both justifications did not result in a suitability of the data presented. The company did not present any evidence to what extent the results of the total population of the study Hong 2012 can be applied to the subpopulation relevant for this benefit assessment.

Regardless of this, it cannot be derived from the available information that the patients in the comparator group had all possibilities of treatment optimization. According to the information, only the dose was to be adjusted and the patients were to use the same formulation of insulin and, if possible, the same treatment regimen throughout the entire study. Correspondingly, only conclusions specifically versus an insulin dose increase and not versus another possibility of insulin optimization could be drawn from this study.

*Further information about the study design and the study populations can be found in Module 4C Section 4.3.1.2 and Appendix 4-G of the dossier, and in Section 2.7.4.4.2 of the full dossier assessment.*

### 2.5.2 Results on added benefit

No relevant data were available for the research question "sitagliptin/metformin plus insulin". Hence the added benefit versus the ACT specified by the G-BA is not proven.

### 2.5.3 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of sitagliptin/metformin plus metformin in comparison with the ACT specified by the G-BA (human insulin plus metformin, or only human insulin if metformin is not tolerated according to the SPC or not sufficiently effective). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result deviates from that of the company, which derived an indication of a considerable added benefit of sitagliptin/metformin plus insulin versus insulin dose increase as a possibility of insulin optimization.

Overall, there is no proof of an added benefit of sitagliptin/metformin plus insulin. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

## 2.6 Extent and probability of added benefit – summary

An overview of the extent and probability of added benefit for the different subindications of sitagliptin/metformin in comparison with the relevant ACTs or versus glipizide plus metformin is given below.

Table 7: Sitagliptin/metformin – extent and probability of added benefit

| Research question | Subindication | Comparator therapy | Extent and probability of added benefit |
|---|---|---|---|
| A1 | Sitagliptin/metformin | Sulfonylurea (glibenclamide, glimepiride) plus metformin | Added benefit not proven[b] |
| A2 | Sitagliptin/metformin | Glipizide plus metformin[a] | Added benefit not proven[b] |
| B | Sitagliptin/metformin plus sulfonylurea | Human insulin plus metformin (Note: only human insulin if metformin is not sufficiently effective) | Added benefit not proven |
| C | Sitagliptin/metformin plus insulin | Human insulin plus metformin (Note: only human insulin if metformin is not tolerated according to the SPC or not sufficiently effective) | Added benefit not proven |

a: According to the commission by the G-BA, direct comparative studies versus glipizide were to be additionally assessed.
b: The company presented the same studies P803 and P024 for these research questions in the dossier assessment on sitagliptin (A13-02), which was prepared at the same time. In case of a proof that the results of both studies do not depend on the metformin dose, the assessment on extent and probability of added benefit cited in the dossier assessment A13-02 could also be used for the fixed combination sitagliptin/metformin.
G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The G-BA decides on added benefit.

*Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.4.9 of the full dossier assessment.*

**References for English extract**

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/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a13_03_sitagliptin/metformin_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.3650.html.*