IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Vildagliptin/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 "Vildagliptin/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
HbA1c	glycosylated haemoglobin
FPG	fasting plasma glucose
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
OAD	oral antidiabetic
RCT	randomized controlled trial
SD	standard deviation
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 drug vildagliptin/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 28 March 2013.

Research question and appropriate comparator therapy

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

Within this therapeutic indication, different subindications for the use of vildagliptin/ 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 vildagliptin/metformin

Research question[a]	Subindication	ACT specified by the G-BA
A1	Vildagliptin/metformin	Sulfonylurea (glibenclamide, glimepiride) plus metformin
A2	Vildagliptin/metformin plus insulin	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)
A3	Vildagliptin/metformin plus sulfonylurea	Human insulin plus metformin (Note: treatment only with human insulin if metformin is not sufficiently effective)
a: Designation corresponds to the coding in the company's dossier. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

For the 3 subindications, the company specified an ACT that was different from the company's point of view (research question A1: sitagliptin plus metformin; research question A2: sitagliptin plus insulin; research question A3: sitagliptin plus metformin plus

sulfonylureas), but did not present any data for these comparisons. Instead, the company's assessment was conducted versus the ACT specified by the G-BA.

Deviations by the company

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

In the subindications "vildagliptin/metformin plus insulin" (research question A2) and "vildagliptin/metformin plus sulfonylurea" (research question A3), the company exclusively chose the comparator therapy "human insulin in combination with metformin". The comparison versus human insulin without metformin was not covered in its respective research question.

Results

Vildagliptin/metformin

The company included 4 direct comparative studies in its assessment (LAF237A2308, LAF237ADE06T, LAF237AFR03 and Jeon 2011). However, all 4 studies were unsuitable for answering the research question.

In the study LAF237A2308, the use of glimepiride did not comply with the recommendations of the Summary of Product Characteristics (SPC). Moreover, it was unclear in the study whether and, if any, how many patients received the metformin dose of at least 1700 mg a day, which concurs with the approval of the fixed combination vildagliptin/metformin.

In the study LAF237ADE06T, all patients were switched to a metformin dose of 2000 mg a day, independent of the metformin dose they had been treated with before. The reason for this was that the fixed combination vildagliptin/metformin without additional administration of metformin was investigated in the study. Hence the study did not answer the present research question.

In the study LAF237AFR03 with the study arms vildagliptin and "conventional treatment with oral antidiabetics [OADs]" (sulfonylureas, glinides, glitazones or acarbose), only 6 out of 22 patients in the comparator arm were treated with the ACT (glimepiride). The allocation to the different OAD treatment options was not conducted randomly. Hence the equal structure of the glimepiride group in comparison with the vildagliptin group was not guaranteed, and the results presented could therefore not be interpreted.

In the study Jeon 2011, patients were included who did not correspond to the research question and glimepiride was not administered in compliance with the approval. In addition, all patients in the study received less than the metformin dose of at least 1700 mg, which is in compliance with the approval of the fixed combination vildagliptin/metformin.

Vildagliptin/metformin plus insulin

The company presented the placebo-controlled study LAF237A23135, from which it only analysed the patients with prior metformin treatment, for the direct comparison of the combination of vildagliptin/metformin plus insulin versus human insulin plus metformin. The study was unsuitable for answering the research question, as it was mostly prohibited to adjust the insulin therapy to individual necessities in the comparator group. The patients were required to continue their prior treatment with insulin unchanged, i.e. the insulin dose had to remain stable during the study, and neither the type of insulin nor the type of insulin therapy were allowed to be changed. Dose adjustments were only permitted if unexpected hypoglycaemias or repeated high levels of fasting plasma glucose (FPG) occurred.

Vildagliptin/metformin plus sulfonylurea

The company identified no studies on vildagliptin/metformin plus sulfonylurea versus the ACT.

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 vildagliptin/metformin compared with the ACT is assessed as follows:

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

Research question	Subindication	ACT	Extent and probability of added benefit
A1	Vildagliptin/metformin	Sulfonylurea[a] plus metformin	Added benefit not proven
A2	Vildagliptin/metformin plus insulin	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)	Added benefit not proven
A3	Vildagliptin/metformin plus sulfonylurea	Human insulin plus metformin (Note: treatment only with human insulin if metformin is not sufficiently effective)	Added benefit not proven
a: Glibenclamide, glimepiride ACT: appropriate comparator therapy; SPC: Summary of Product Characteristics			

[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].

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 vildagliptin/metformin was conducted according to the SPC [3] for the treatment of adult patients with type 2 diabetes mellitus in the following subindications:

- **Vildagliptin/metformin:** treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets.
- **Vildagliptin/metformin plus sulfonylurea:** in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulfonylurea.
- **Vildagliptin/metformin plus insulin:** in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.

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

Table 4: Subindications and ACT for vildagliptin/metformin

Research question[a]	Subindication	ACT specified by the G-BA
A1	Vildagliptin/metformin	Sulfonylurea (glibenclamide, glimepiride) plus metformin
A2	Vildagliptin/metformin plus insulin	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)
A3	Vildagliptin/metformin plus sulfonylurea	Human insulin plus metformin (Note: treatment only with human insulin if metformin is not sufficiently effective)
a: Designation corresponds to the coding in the company's dossier. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

The company specified a comparator therapy that was appropriate from the company's point of view for all 3 subindications mentioned (research question A1: sitagliptin plus metformin; research question A2: sitagliptin plus insulin; research question A3: sitagliptin plus metformin plus sulfonylureas), but did not present any data for these comparisons.

The alternative comparator therapy cited by the company was not considered any further in the benefit assessment (see Section 2.7.1 of the full dossier assessment).

Research question A1: vildagliptin/metformin

The ACT specified by the G-BA (metformin plus sulfonylurea [glibenclamide, glimepiride] was used for this subindication.

In its dossier, the company concurred with the ACT specified by the G-BA as an auxiliary measure.

Research question A2: vildagliptin/metformin plus insulin

The ACT specified by the G-BA (human insulin plus metformin, if applicable only human insulin if metformin is not tolerated according to the SPC or not sufficiently effective) was used for this subindication.

Alternatively, the company referred to human insulin plus metformin as ACT in its dossier. Hence no data were available and no information was given on the comparison with human insulin (without metformin). The company did not provide any reasons for this deviation.

Research question A3: vildagliptin/metformin plus sulfonylurea

The ACT specified by the G-BA (human insulin plus metformin, if applicable only human insulin if metformin is not sufficiently effective) was used for this subindication.

Alternatively, the company referred to human insulin plus metformin as ACT in its dossier. Hence no data were available and no information was given on the comparison with human insulin (without metformin). The company did not provide any reasons for this deviation.

Summary

The assessment of vildagliptin/metformin in the different subindications was conducted versus the ACTs specified by the G-BA. The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs) with a minimum duration of 24 weeks.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.2.1, 2.7.2.2, 2.7.3.1, 2.7.3.2 and 2.7.4 of the full dossier assessment.

2.3 Research question A1: vildagliptin/metformin

2.3.1 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 vildagliptin/metformin (studies completed up to 19 February 2013)
- Bibliographical literature search on vildagliptin/metformin (last search on 6 February 2013)
- Search in trial registries for studies on vildagliptin/metformin (last search on 5 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 relevant studies suitable for assessing the added benefit of vildagliptin/metformin were identified from the steps of information retrieval mentioned. In contrast, the company included 4 direct comparative studies (LAF237A2308 [4], LAF237ADE06T [5], LAF237AFR03 [6] and Jeon 2011 [7]). However, all 4 studies were unsuitable for answering the research question.

Table 5 shows the characteristics of these studies and Table 6 a description of the intervention. Table 7 summarizes the reasons for exclusion.

Table 5: Characteristics of the studies included by the company – RCT, direct comparison: vildagliptin/metformin vs. sulfonylurea (glimepiride) plus metformin

Study	Study design	Study duration	Population	
			Type of prior treatment	Criteria for inadequate glycaemic control
LAF237A2308	RCT, double-blind, double-dummy, parallel, multicentre	Screening phase: 4 weeks Treatment: 104 weeks	Patients with type 2 diabetes mellitus (18-73 years) with inadequate monotherapy with metformin (with maximum tolerated dose of at least 1500 mg a day, stable for at least 3 months)	HbA1c > 6.5% and ≤ 8.5%
LAF237ADE06T	RCT, open-label, parallel, monocentre	Screening phase: 14 days Treatment: 24 weeks	Patients with type 2 diabetes mellitus (30-80 years) with inadequate monotherapy with metformin (at maximum or maximum tolerated dose, stable for at least 3 months) with indication for treatment with an additional drug according to the judgment by the treating doctor	HbA1c > 6.5% and ≤ 9.5%; patients with pre-existing cardiovascular conditions (coronary heart disease or myocardial infarction) with HbA1c of > 7.0% and ≤ 9.5%
LAF237AFR03	RCT, open-label, parallel, multicentre	24 weeks	Older patients with type 2 diabetes mellitus (65-80 years) with inadequate monotherapy with metformin (with maximum tolerated dose in the last 3 months)	HbA1c > 6.5% or > 7% (depending on the individual treatment goal of the patient) and ≤ 8.5% at the first study visit
Jeon 2011	RCT, open-label, parallel, monocentre	32 weeks	Patients with type 2 diabetes mellitus: treatment-naive or with monotherapy (OADs, e.g. glimepiride [2 to 4 mg] or metformin [500 to 1000 mg] for < 6 months) Pretreated patients had to undergo a wash-out period of at least 2 weeks.	HbA1c > 7%
HbA1c: glycosylated haemoglobin; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus				

Table 6: Characteristics of the intervention of the studies included by the company – RCT, direct comparison: vildagliptin/metformin vs. sulfonylurea (glimepiride) plus metformin

Study	Intervention Number of patients	Comparator Number of patients
LAF237A2308	▪ Vildagliptin 50 mg (twice a day) tablets (morning/evening) + metformin in a stable maximum tolerated dose of at least 1500 mg a day + glimepiride placebo ▪ N = 1562	▪ Glimepiride 2-6 mg (once a day) capsules (morning) + metformin in a stable maximum tolerated dose of at least 1500 mg a day + vildagliptin placebo ▪ Initial dose 2 mg; titration to the next dose level (4 mg, 6 mg a day) in week 4 and 8 or at every subsequent study visit, if FPG > 112 mg/dl or fasting blood glucose > 100 mg/dl and no contraindication to titration due to risk of hypoglycaemia ▪ N = 1556
LAF237ADE06T	▪ Vildagliptin 50 mg/metformin[a] 1000 mg fixed combination (twice a day) ▪ N = 22	▪ Glimepiride 1-4 mg (once a day) + metformin[a] 1000 mg (twice a day) ▪ Dose was specified individually according to the necessities of the patient and titrated at an interval of 1-2 weeks ▪ N = 23
LAF237AFR03	▪ Vildagliptin 50 mg (twice a day) + metformin at previous dosage ▪ N = 24	▪ All other OADs ("conventional therapy") that can be prescribed in combination with metformin (sulfonylureas, glinides, glitazones, acarbose according to the recommendations by the Haute Autorité de Santé 2006) ▪ N = 22 (thereof glimepiride n = 6)
Jeon 2011	▪ Vildagliptin 50 mg (twice a day) + metformin 500 mg (twice a day) ▪ N = 51	▪ Glimepiride 2 mg (twice a day) + metformin 500 mg (twice a day) ▪ Treatment with glimepiride and metformin was down-titrated during the follow-up period in case of recurring hypoglycaemias ▪ N = 51

a: Change of methods after the start of the study due to intolerance of the metformin dose of 1000 mg (twice a day) in some patients: At the treating doctor's discretion, the metformin dose of 1000 mg (twice a day) could be lowered to 850 mg (twice a day).

FPG: fasting plasma glucose; N: number of randomized patients;OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus

Table 7: Overview of the reasons for exclusion of the studies – direct comparison: vildagliptin/metformin vs. sulfonylurea (glimepiride) plus metformin

Study	Reasons for exclusion			
	Study design	Population (type of prior treatment)	Intervention	Comparator therapy
LAF237A2308			●	●
LAF237ADE06T		○	●	●
LAF237AFR03	●			●
Jeon 2011		●	●	●

●: reason for exclusion; ○: uncertain; vs.: versus

The study LAF237A2308 [4] was unsuitable for answering the present research question for the following reasons:

- The relevant target population for the approved therapeutic indication had to have received an intervention of at least 1700 mg of metformin a day because a dose of at least 1700 mg of metformin a day is also administered with the fixed combination vildagliptin/metformin. However, the company did not present any results for this target population. It remained unclear how many patients of the relevant target population received at least 1700 mg of metformin. The available data on location and dispersion parameters do not allow to reconstruct the proportion of patients who received a lower dose than 1700 mg. Scenarios are conceivable, for example, in which the proportion of these patients is as high as 30% or even 40%.
- The administration of glimepiride did not comply with the recommendations provided in the SPC [8]. The initial dose of glimepiride was 2 mg a day and was up-titrated by 2 mg in intervals of 4 weeks during the first 8 weeks of the treatment phase as long as the fasting blood glucose levels were above 100 mg/dl. The SPC recommends an initial dose of 1 mg a day and a dose increase in 1 mg steps every 1 to 2 weeks under close medical supervision. So the titration was conducted considerably more rapidly than recommended, particularly considering the very low target level (fasting blood glucose ≤ 100 mg/dl). Moreover, titration based on target blood glucose levels was only performed in the glimepiride group, but not in the vildagliptin group with a blood-glucose lowering drug. Hence the study LAF237A2308 [4] did not represent a comparison of the two drugs alone, but of two combined interventions (treatment regimen with different treatment goals plus drug).

Additionally it should be pointed out that the HbA1c (glycosylated haemoglobin) value (long-term marker for the average blood-glucose level) had a mean value of 7.3% (standard deviation [SD] = 0.65) in the total population at the start of the study. 50% of the patients had an HbA1c value of ≤ 7.2%. According to current knowledge, for a relevant proportion of patients one cannot assume inadequate glycaemic control that would have required intensified therapy. Particularly in these patients, intensified blood-glucose lowering therapy was associated with an increased risk of hypoglycaemia.

The study LAF237ADE06T [5] was unsuitable for assessing the present research question for the following reasons:

- Patients were enrolled in the study who did not achieve adequate glycaemic control despite metformin monotherapy in a "stable, maximum or maximum tolerated dose". There was no information on the dosage of the metformin treatment of the patients before randomization. After randomization, all patients were treated with a daily dose of 2000 mg of metformin, independent from the metformin dose they were treated with before (because the fixed combination without additional administration of metformin was used here). The study documents did not provide information about whether it was envisaged to limit the study population to patients whose maximum tolerated dose was exactly 2000 mg of metformin. It cannot be assumed that all patients had been treated with exactly 2000 mg of metformin, but also with considerably higher or lower daily doses. Hence the study did not answer the present research question.

The study LAF237AFR03 [6] was unsuitable for assessing the present research question for the following reasons:

- The patients were randomly assigned either to the study arm with vildagliptin or to the one with conventional treatment with OADs. After randomization in the study arm "conventional treatment", the treating doctor chose, at his or her own discretion, among the following OADs: sulfonylureas, glinides, glitazones or acarbose. Only 6 of the 22 patients received the ACT (glimepiride). The company only presented the results of these 6 patients in the comparator arm for the present research question. Since the allocation to the different OAD treatment options was not conducted at random, the equal structure of the glimepiride group in comparison with the vildagliptin group was no longer guaranteed, and the results could therefore no longer be interpreted.

The study Jeon 2011 [7] was unsuitable for answering the present research question for the following reasons:

- Both treatment-naive patients and patients who had already been treated with OAD monotherapy (glimepiride or metformin) for less than 6 months were enrolled in the study. Treatment-naive patients and patients who have been treated with glimepiride do not correspond to the target population. Those patients who had been pretreated with

metformin had only received a daily dose of 500 mg to 1000 mg in their prior treatment. This corresponds to only 17% to 33% of the maximum approved dose of metformin. It is assumed that this was not the maximum tolerated dose of metformin for a relevant proportion of patients so that these patients also did not correspond to the target population.

- The patients received 1000 mg of metformin a day during treatment. However, when the fixed combination vildagliptin/metformin is used, the patients receive at least 1700 mg of metformin a day.
- The patients received an initial dose of glimepiride of 4 mg a day after the start of the study. This does not comply with the approval (at least for those patients who were not pretreated with glimepiride) [8].

Summary

Overall, there were no studies that would have been suitable for assessing the added benefit of vildagliptin/metformin versus the ACT "sulfonylurea plus metformin".

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.2 and 2.7.2.4.1 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 of the dossier, and in Sections 2.7.2.4 and 2.7.2.4.2 of the full dossier assessment.

2.3.2 Results on added benefit

There were no relevant data for vildagliptin/metformin in the dual combination. Hence the added benefit of vildagliptin/metformin versus the ACT specified by the G-BA is not proven in this research question.

2.3.3 Extent and probability of added benefit

No proof of added benefit of vildagliptin/metformin 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 a considerable added benefit (which could be "safely assumed", according to the company) of vildagliptin/ metformin.

2.4 Research question A2: vildagliptin/metformin plus insulin

2.4.1 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 vildagliptin/metformin plus insulin (studies completed up to 19 February 2013)
- Bibliographical literature search on vildagliptin/metformin plus insulin (last search on 6 February 2013)
- Search in trial registries for studies on vildagliptin/metformin plus insulin (last search on 5 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 relevant studies suitable for assessing the added benefit of vildagliptin/metformin plus insulin in comparison with the ACT for the present research question were identified from the steps of information retrieval mentioned. In contrast, the company included a direct comparative study (LAF237A23135 [9]). However, this study was unsuitable for answering the research question.

Table 8 shows the characteristics of the study LAF237A23135 and Table 9 a description of the intervention.

Table 8: Characteristics of the studies included by the company – RCT, direct comparison: vildagliptin/metformin plus insulin vs. human insulin plus metformin

Study	Study design	Study duration	Population	
			Type of prior treatment	Criteria for inadequate glycaemic control
LAF237-A23135	RCT, double-blind, parallel	24 weeks	Adult patients (18-80 years) with type 2 diabetes mellitus with stable insulin dose (≤ 1 unit/kg/day once or twice a day for at least 12 weeks), with or without metformin treatment (stable for at least 12 weeks with at least 1500 mg a day or at a maximum tolerated dose) and inadequate glycaemic control	HbA1c ≥ 7.5 and ≤ 11%

HbA1c: glycosylated haemoglobin; RCT: randomized controlled trial; vs.: versus

Table 9: Characteristics of the interventions – RCT, direct comparison: vildagliptin/metformin plus insulin vs. human insulin plus metformin

Study	Intervention Number of patients	Comparator Number of patients
LAF237-A23135	▪ Vildagliptin 50 mg twice a day + insulin ▪ ± metformin at previous dosage (maintained stable) ▪ Total population: N= 228, thereof metformin subpopulation[a]: n = 139	▪ Placebo twice a day + insulin ▪ ± metformin at previous dosage (maintained stable) ▪ Total population: N= 221, thereof metformin subpopulation[a]: n = 137
	Treatment with insulin ▪ Continuation of previous insulin therapy ▪ Insulin dose had to remain stable during the study (i.e. remain within the range of a 10% increase compared with baseline) without changing treatment frequency or the type of insulin (except dose adjustments for safety reasons at the treating doctor's discretion) ▪ Dose adjustments in both directions could only be conducted in case of safety risks at the treating doctor's discretion.	

a: This subpopulation is the target population shown in the dossier. It consists of patients who were pretreated with insulin and with metformin and whose stable treatment was maintained stable (taking into account the possible adjustments mentioned above) after randomization.

N: number of randomized patients, n: number of patients in the subpopulation, RCT: randomized controlled trial; vs.: versus

In their prior treatment, patients received a basal, long-acting, intermediate insulin alone or in a premixed combination with a rapid- or short-acting insulin and metformin in a dose of at least 1500 mg a day. Both prior treatments had to be stable for at least 12 weeks before the start of the study and without achieving adequate glycaemic control.

The study LAF237A23135 [9] was unsuitable for assessing the added benefit, as it was mostly prohibited to adjust the insulin therapy to individual necessities in the comparator group. Patients in both treatment arms were required to continue their prior treatment with insulin and metformin unchanged, i.e. it was neither allowed to change the type of insulin nor the type of insulin therapy. The insulin dose had to remain stable during the study (i.e. remain within a range of a 10% dose increase compared with baseline). Further dose adjustments could only be conducted if unexpected hypoglycaemias or repeated high levels of FPG occurred. Antidiabetic therapy would usually already be optimized in less pronounced fluctuations of blood glucose levels so that hypoglycaemia and hyperglycaemia do not occur in the first place, and not only as a reaction to these events. Because of the lack of opportunities for optimization – particularly in the comparator group – the study was unsuitable for drawing conclusions on the added benefit of vildagliptin/metformin plus insulin versus the ACT (human insulin with or without metformin). To draw conclusions on the added benefit, the administration of vildagliptin/metformin plus insulin would have to be compared with other optimization strategies such as optimizing insulin therapy including changing the type or regimen of the insulin.

Additionally it should be pointed out that it was unclear which proportion of the patients was treated with the minimum dose of 1700 mg of metformin and thus in compliance with the approval of the fixed combination vildagliptin/metformin plus insulin. Because of the company's approach not to present data for this target population, the study could not be used for assessing the added benefit of vildagliptin/metformin in the present research question.

Summary

Overall, no relevant data were available for the assessment of the added benefit of vildagliptin/metformin plus insulin versus the ACT.

Further information about the result of information retrieval and the resulting study pool can be found in Module 4, Section 4.3.1.1 of the dossier, and in Section 2.7.3.4 of the full dossier assessment.

2.4.2 Results on added benefit

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

Further information about the results on added benefit can be found in Module 4A Sections 4.4.1 and 4.4.2 of the dossier, and in Section 2.7.2.9.2 of the full dossier assessment.

2.4.3 Extent and probability of added benefit

No proof of added benefit of vildagliptin/metformin plus insulin 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 a minor added benefit (which could be "safely assumed", according to the company) of vildagliptin/metformin plus insulin.

2.5 Research question A3: vildagliptin/metformin plus sulfonylurea

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 vildagliptin/metformin/sulfonylureas (studies completed up to 19 February 2013)
- Bibliographical literature search on vildagliptin/metformin/sulfonylureas (last search on 6 February 2013)
- Search in trial registries for studies on vildagliptin/metformin/sulfonylureas (last search on 5 February 2013)
- Study list on vildagliptin/metformin/sulfonylureas for indirect comparisons (studies completed up to 16 November 2012)
- Bibliographical literature search on human insulin plus metformin (last search on 5 February 2013)
- Search in trial registries for studies on human insulin plus metformin (last search on 10 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)

The company did not identify any relevant study from the steps of information retrieval mentioned.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier. Further information about the result of information retrieval and the resulting study pool can be found in Module 4, Section 4.3.1.1 of the dossier.

2.5.2 Results on added benefit

There were no relevant data for the subindication of vildagliptin/metformin plus sulfonylurea. Hence the added benefit versus the ACT specified by the G-BA is not proven for the present research question.

2.5.3 Extent and probability of added benefit

Since no relevant studies were presented for the benefit assessment, there is no proof of an added benefit of vildagliptin/metformin plus sulfonylurea in comparison with the ACT specified by the G-BA. Hence there are no patient groups for whom a therapeutically important added benefit could be derived.

This assessment concurs with that of the company in so far as no studies for a direct comparison were included in the dossier and no indirect comparison was possible. Hence the added benefit could not be derived on the basis of the data (referred to as "non-quantifiable" in the dossier).

2.6 Extent and probability of added benefit - summary

An overview of the extent and probability of added benefit for the different subindications of vildagliptin/metformin in comparison with the relevant ACTs is given below:

Table 10: Vildagliptin/metformin – extent and probability of added benefit

Research question	Subindication	ACT	Extent and probability of added benefit
A1	Vildagliptin/metformin	Sulfonylurea[a] plus metformin	Added benefit not proven
A2	Vildagliptin/metformin plus insulin	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)	Added benefit not proven
A3	Vildagliptin/metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)	Added benefit not proven
a: Glibenclamide, glimepiride ACT: appropriate comparator therapy; 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 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_17_vildagliptin/metformin_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.3639.html