

IQWiG Reports – Commission No. A13-16

**Vildagliptin –
Benefit assessment according
to § 35a Social Code Book V¹**

Extract

¹ Translation of Sections 2.1 to 2.8 of the dossier assessment “Vildagliptin – Nutzenbewertung gemäß § 35a SGB V” (Version 1.0; Status: 27 June 2013). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Vildagliptin – Benefit assessment according to § 35a Social Code Book V

Contracting agency:

Federal Joint Committee

Commission awarded on:

28 March 2013

Internal Commission No.:

A13-16

Address of publisher:

Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0

Fax: +49 (0)221 – 35685-1

E-Mail: berichte@iqwig.de

Internet: www.iqwig.de

Medical and scientific advice:

- Andreas Fritsche, Institute for Diabetes Research and Metabolic Diseases, University Hospital Tübingen, Germany

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

IQWiG employees involved in the dossier assessment:²

- Sebastian Werner
- Thomas Kaiser
- Petra Kohlepp
- Tatjana Kvitkina
- Stefan K. Lhachimi
- Stefanie Reken
- Christoph Schürmann
- Guido Skipka
- Siw Waffenschmidt
- Min Zhou

Keywords: vildagliptin, diabetes mellitus – type 2, benefit assessment

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

Table of contents

	Page
List of tables	iv
List of figures	v
List of abbreviations	vi
2 Benefit assessment	1
2.1 Executive summary of the benefit assessment	1
2.2 Research questions	5
2.3 Research question A1: monotherapy with vildagliptin	8
2.3.1 Information retrieval and study pool	8
2.3.2 Results on added benefit.....	12
2.3.3 Extent and probability of added benefit	12
2.4 Research question A2: combination of vildagliptin plus metformin	13
2.4.1 Information retrieval and study pool	13
2.4.2 Results on added benefit.....	18
2.4.3 Extent and probability of added benefit	18
2.5 Research question A3: combination of vildagliptin plus sulfonyleurea	19
2.5.1 Information retrieval and study pool	19
2.5.2 Results on added benefit.....	19
2.5.3 Extent and probability of added benefit	19
2.6 Research question A4: Combination of vildagliptin plus insulin (with or without metformin)	21
2.6.1 Information retrieval and study pool	21
2.6.2 Results on added benefit.....	29
2.6.3 Extent and probability of added benefit	29
2.7 Research question A5: combination of vildagliptin plus sulfonyleurea plus metformin	30
2.7.1 Information retrieval and study pool	30
2.7.2 Results on added benefit.....	30
2.7.3 Extent and probability of added benefit	31
2.8 Extent and probability of added benefit - summary	32
References for English extract	32

List of tables³

	Page
Table 2: Subindications and ACT for vildagliptin	1
Table 3: Vildagliptin – extent and probability of added benefit	4
Table 4: Subindications and ACT for vildagliptin	5
Table 5: Characteristics of the studies included by the company – indirect comparison: vildagliptin vs. glimepiride	9
Table 6: Characteristics of the interventions – indirect comparison: vildagliptin vs. glimepiride	10
Table 7: Overview of the reasons for exclusion of the studies – indirect comparison: vildagliptin vs. glimepiride	11
Table 8: Characteristics of the studies included by the company – RCT, direct comparison: combination of vildagliptin plus metformin vs. sulfonylurea (glimepiride) plus metformin	14
Table 9: Characteristics of the intervention of the studies included by the company – RCT, direct comparison: combination of vildagliptin plus metformin vs. sulfonylurea (glimepiride) plus metformin	15
Table 10: Overview of the reasons for exclusion of the studies – direct comparison: vildagliptin plus metformin vs. sulfonylurea (glimepiride) plus metformin.....	16
Table 11: Characteristics of the studies included by the company – RCT, direct comparison: vildagliptin plus insulin plus metformin vs. human insulin plus metformin.....	22
Table 12: Characteristics of the interventions – RCT, direct comparison: vildagliptin plus insulin plus metformin vs. human insulin plus metformin.....	22
Table 13: Characteristics of the studies on the comparator therapy included by the company – indirect comparison: vildagliptin plus insulin vs. insulin plus metformin	25
Table 14: Characteristics of the interventions – indirect comparison: vildagliptin plus insulin vs. insulin plus metformin	26
Table 15: Overview of the reasons for exclusion of the studies on the ACT – indirect comparison: combination of vildagliptin plus insulin vs. insulin plus metformin.....	28
Table 16: Vildagliptin – extent and probability of added benefit	32

³ Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of figures

	Page
Figure 1: Network structure of the indirect comparison of vildagliptin plus insulin vs. insulin plus metformin presented in the dossier	24

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
FPG	fasting plasma glucose
G-BA	<i>Gemeinsamer Bundesausschuss</i> (Federal Joint Committee)
HbA1c	glycosylated haemoglobin
IQWiG	<i>Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen</i> (Institute for Quality and Efficiency in Health Care)
OAD	oral antidiabetic
RCT	randomized controlled trial
SD	standard deviation
SGB	<i>Sozialgesetzbuch</i> (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. 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 vildagliptin was conducted according to the approval 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 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

Research question ^a	Subindication	ACT specified by the G-BA
A1	Monotherapy with vildagliptin	Sulfonylurea (glibenclamide, glimepiride)
A2	Vildagliptin plus metformin	Sulfonylurea (glibenclamide, glimepiride) plus metformin
A3	Vildagliptin plus sulfonylurea	Human insulin in combination with sulfonylurea (glibenclamide, glimepiride), if applicable only treatment with human insulin
A4	Vildagliptin plus insulin (with or without metformin)	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)
A5	Vildagliptin plus sulfonylurea plus metformin	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 all 5 subindications, the company specified an ACT that was different from the company's point of view (research question A1: sitagliptin; research question A2: sitagliptin plus metformin; research question A3: sitagliptin plus sulfonylureas; research question A4: sitagliptin plus insulin; research question A5: 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 the subindication "monotherapy with vildagliptin" (research question A1), the company did not limit the study inclusion to studies with the approval-compliant patient population (i.e. patients in whom diet and exercise alone do not provide adequate treatment and for whom metformin is unsuitable due to contraindications or intolerance).

In the subindication "vildagliptin plus sulfonylurea" (research question A3), the company exclusively chose the comparator therapy "human insulin in combination with sulfonylurea (glibenclamide, glimepiride)". The comparison versus human insulin without sulfonylurea was not covered in its research question.

In the subindications "vildagliptin plus insulin (with or without metformin)" (research question A4) and "vildagliptin plus sulfonylurea plus metformin" (research question A5), 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

Monotherapy with vildagliptin

There was no study on the direct comparison with the ACT for the research question on the monotherapy with vildagliptin.

The company conducted an indirect comparison of vildagliptin versus glimepiride using the common comparator gliclazide, for which it presented 3 studies. One study (LAF237A2310) compared vildagliptin with gliclazide, 2 studies compared glimepiride with gliclazide (GUIDE, Kaneko 1993). The 3 studies presented were unsuitable for answering the present research question, partly because they were not conducted in the relevant patient population. The inclusion and exclusion criteria of these studies did not provide any information about whether the patients had metformin intolerance or contraindications. The company did not make any statement on the approval compliance of the study population. The company did also not prove the transferability of the results. There are additional reasons for the non-usability of the studies in the indirect comparison presented, e.g. the considerably lower dosage of gliclazide in the study Kaneko 1993 in comparison with the study LAF237A2310.

Combination of vildagliptin plus metformin

The company presented 4 studies on the direct comparison of vildagliptin plus metformin versus glimepiride plus metformin (LAF237A2308, LAF237ADE06T, LAF237AFR03 and Jeon 2011). The 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). 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 [OAD]" (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 structural equality 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. Moreover, glimepiride was not used in accordance with its approval in the study.

Combination of vildagliptin plus sulfonylurea

The company identified no studies on the combination of vildagliptin plus sulfonylurea versus the ACT.

Combination of vildagliptin plus insulin (with or without metformin)

The company presented data both for a direct comparison and for an indirect comparison for this research question.

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 plus insulin (with metformin) 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.

The company presented 9 studies in total for the indirect comparison of the combination of vildagliptin plus insulin (without metformin) versus human insulin plus metformin using the common comparator insulin. On the side of the intervention, the company included the placebo-controlled study LAF237A23135, which it had already used for the direct comparison, but this time only analysed the patients without metformin treatment. On the side of the comparator therapy "human insulin plus metformin", the company identified 8 studies, which were relevant from the company's point of view, for the indirect comparison (Civera 2008, Vähätalo 2007, Yilmaz 2007, Ryysy 2001, Mäkimattila 1999, Aviles-Santa 1999, Douek 2005, Giugliano 1993). The 8 studies presented on the comparator therapy presented were unsuitable for the indirect comparison, partly because the respective common comparator was not comparable with the study LAF237A23135, and therefore did not fulfil

the assumption of similarity – a precondition for an adjusted indirect comparison and the interpretability of the results. In addition, a patient population was studied that did not correspond to the research question in 5 of the 8 studies. Moreover, it was not possible to adjust the insulin type or regimen in 6 of the 8 studies.

Combination of vildagliptin plus sulfonylurea plus metformin

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

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

On the basis of the results, the extent and probability of the added benefit of vildagliptin compared with the ACT is assessed as follows:

Table 3: Vildagliptin – extent and probability of added benefit

Research question	Subindication	ACT	Extent and probability of added benefit
A1	Monotherapy with vildagliptin	Sulfonylurea ^a	Added benefit not proven
A2	Vildagliptin plus metformin	Sulfonylurea ^a plus metformin	Added benefit not proven
A3	Vildagliptin plus sulfonylurea	Human insulin in combination with sulfonylurea ^a , if applicable only treatment with human insulin	Added benefit not proven
A4	Vildagliptin plus insulin (with or without metformin)	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
A5	Vildagliptin plus sulfonylurea plus metformin	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			

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.

⁴ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research questions

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

- **Monotherapy with vildagliptin:** in patients in whom diet and exercise alone do not provide adequate treatment and for whom metformin is unsuitable due to contraindications or intolerance.
- **Combination of vildagliptin plus metformin:** in patients with inadequate glycaemic control despite monotherapy with maximum tolerated doses of metformin.
- **Combination of vildagliptin plus sulfonylurea:** in patients with inadequate glycaemic control despite monotherapy with maximum tolerated doses of a sulfonylurea and for whom metformin is unsuitable due to contraindications or intolerance.
- **Combination of vildagliptin plus insulin (with or without metformin):** in patients in whom diet and exercise in addition to a stable insulin dose do not provide adequate glycaemic control.
- **Combination of vildagliptin plus sulfonylurea plus metformin:** in patients in whom diet and exercise in addition to a dual therapy with sulfonylurea and metformin do not provide adequate glycaemic control.

Moreover, vildagliptin 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 vildagliptin

Research question ^a	Subindication	ACT specified by the G-BA
A1	Monotherapy with vildagliptin	Sulfonylurea (glibenclamide, glimepiride)
A2	Vildagliptin plus metformin	Sulfonylurea (glibenclamide, glimepiride) plus metformin
A3	Vildagliptin plus sulfonylurea	Human insulin in combination with sulfonylurea (glibenclamide, glimepiride), if applicable only treatment with human insulin
A4	Vildagliptin plus insulin (with or without metformin)	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)
A5	Vildagliptin plus sulfonylurea plus metformin	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 5 subindications mentioned (research question A1: sitagliptin; research question A2: sitagliptin plus metformin; research question A3: sitagliptin plus sulfonyleureas; research question A4: sitagliptin plus insulin; research question A5: sitagliptin plus metformin plus sulfonyleureas), but did not present any data for these comparisons. The alternative comparator therapies cited by the company were not considered any further in the benefit assessment (see Section 2.9.1 of the full dossier assessment).

Research question A1: monotherapy with vildagliptin

The ACT specified by the G-BA (sulfonyleurea [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: combination of vildagliptin plus metformin

The ACT specified by the G-BA (metformin plus sulfonyleurea [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 A3: combination of vildagliptin plus sulfonyleurea

The ACT specified by the G-BA (human insulin in combination with sulfonyleurea [glibenclamide, glimepiride], if applicable only treatment with human insulin) was used for this subindication.

The company only partially concurred with the G-BA's specification, and alternatively exclusively chose the comparator therapy in combination with sulfonyleurea (glibenclamide, glimepiride). The comparison versus human insulin without sulfonyleurea was not covered in its research question. It did not provide any reasons for this deviation.

Research question A4: combination of vildagliptin plus insulin (with or without metformin)

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 A5: combination of vildagliptin plus sulfonylurea plus metformin

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 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 2.9.2.1, 2.9.2.2, 2.9.3.1, 2.9.3.2, 2.9.4, 2.9.5.1, 2.9.5.2 and 2.9.6 of the full dossier assessment.

2.3 Research question A1: monotherapy with vildagliptin

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 (studies completed up to 19 February 2013)
- Bibliographical literature search on vildagliptin (last search on 6 February 2013)
- Search in trial registries for studies on vildagliptin (last search on 5 February 2013)
- Study list on vildagliptin for indirect comparisons (studies completed up to 16 November 2012)
- Bibliographical literature search on sulfonylureas (glibenclamide: last search on 6 February 2013; glimepiride: last search on 7 February 2013)
- Search in trial registries for studies on sulfonylureas (glibenclamide, glimepiride) (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 data presented by the company were unsuitable to draw conclusions on the added benefit of the monotherapy with vildagliptin versus the ACT. This is justified below.

Direct comparisons

The company did not present any studies on the direct comparison with the ACT for the research question on the monotherapy with vildagliptin.

Indirect comparisons

The company conducted an adjusted indirect comparison of vildagliptin versus glimepiride, for which it presented 3 studies. One study (LAF237A2310 [5]) compared vildagliptin with gliclazide, 2 studies compared the ACT (glimepiride) with the common comparator gliclazide (GUIDE [6], Kaneko 1993 [7]). One additional study, which provided data on the comparison of glibenclamide versus gliclazide [8], was not included in the indirect comparison by the company because the company had chosen glimepiride instead of glibenclamide as ACT.

The 3 studies presented were unsuitable for answering the present research question. Table 5 shows the main characteristics of the studies and Table 6 a description of the interventions. Table 7 summarizes the reasons for exclusion.

Table 5: Characteristics of the studies included by the company – indirect comparison: vildagliptin vs. glimepiride

Comparison Study	Study design	Study duration	Population	
			Type of prior treatment	Criteria for inadequate glycaemic control
Vildagliptin vs. gliclazide				
LAF237A2310	RCT, double-blind, parallel	104 weeks	Adult patients (≥ 18 years) with type 2 diabetes mellitus with inadequate glycaemic control despite diet and physical exercise, without treatment with OADs for ≥ 12 weeks before the start of the study and at any time in the past for > 3 consecutive months.	HbA1c 7.5%–11%
Glimepiride vs. gliclazide				
GUIDE	RCT, double-blind, parallel	27 weeks	Adult patients (> 35 years) with type 2 diabetes mellitus, so far only treated with diet alone or additionally with metformin or an α -glucosidase inhibitor (≥ 3 months)	HbA1c 6.9%–11.5%
Kaneko 1993	RCT, double-blind, parallel	24 weeks	Adult patients (20-79 years) with type 2 diabetes mellitus, so far treated with diet alone or additionally with a sulfonylurea (not glimepiride or gliclazide)	HbA1c 7.0%–9.9%; fasting blood glucose at two points in time within 12 weeks before the start of the study: 140–180 mg/dl
HbA1c: glycosylated haemoglobin; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus				

Table 6: Characteristics of the interventions – indirect comparison: vildagliptin vs. glimepiride

Comparison Study	Intervention Number of patients	Common comparator Number of patients
Vildagliptin vs. gliclazide		
LAF237A2310	<ul style="list-style-type: none"> ▪ Vildagliptin 50 mg twice a day + gliclazide placebo ▪ Titration with the non-glucose-lowering substance placebo in the first 12 weeks of the treatment analogous to the procedure in the comparator group (pseudotitration) ▪ Rescue treatment with metformin in/after week 24 in case of inadequate therapeutic effect ▪ N = 546 	<ul style="list-style-type: none"> ▪ Gliclazide 80-320 mg (once a day up to 160 mg or twice a day > 160 mg) + vildagliptin placebo twice a day ▪ Initial dose 80 mg a day; titration to the next dose level (160 mg, 240 mg, 320 mg a day) in week 4, 8 and 12, if FPG > 126 mg/dl or fasting blood glucose > 113 mg/dl and no contraindication to titration due to risk of hypoglycaemia ▪ Rescue treatment with metformin in/after week 24 in case of inadequate therapeutic effect ▪ N = 546
Glimepiride vs. gliclazide		
GUIDE	<ul style="list-style-type: none"> ▪ Glimepiride 1-6 mg once a day ▪ Initial dose 1 mg a day; titration every 3 weeks (9 weeks titration period) to the next dose level with the therapeutic goal of an FPG of 90 to 140 mg/dl ▪ Total population: N = 440, of which patients^b who had only been pretreated with diet: n = 150 	<ul style="list-style-type: none"> ▪ Gliclazide MR^a 30–120 mg once a day ▪ Initial dose 30 mg a day; titration every 3 weeks (9 weeks titration period) to the next dose level with the therapeutic goal of an FPG of 90 to 140 mg/dl ▪ Total population: N = 405, of which patients^b who had only been pretreated with diet: n = 129
Kaneko 1993	<ul style="list-style-type: none"> ▪ Glimepiride 1-6 mg (once a day up to 3 mg or twice a day > 3 mg) + gliclazide placebo ▪ Initial dose 1 mg a day; dose was generally increased every 4 weeks adjusted in such a way that the blood glucose of the patient approximated normal levels^b as much as possible ▪ Total population: N = 230, of which patients who had only been pretreated with diet: n = 44 	<ul style="list-style-type: none"> ▪ Gliclazide 40-160 mg (once a day up to 120 mg or twice a day > 120 mg) + glimepiride placebo ▪ Initial dose 40 mg a day; dose was generally increased every 4 weeks adjusted in such a way that the blood glucose of the patient approximated normal levels^b as much as possible ▪ Total population: N = 229, of which patients who had only been pretreated with diet: n = 47
<p>a: Gliclazide MR 30-120 mg and gliclazide 80-320 mg are dose equivalent.</p> <p>b: Patients who were only treated with glimepiride or gliclazide monotherapy after randomization and did not receive any concomitant medication with metformin or other OADs.</p> <p>b: Normal levels for blood-glucose-based therapy during the study not defined in the translation of the publication available.</p> <p>FPG: fasting plasma glucose; MR: modified release; N: number of randomized patients; n: number of patients (intention-to-treat population); OAD: oral antidiabetic; vs.: versus</p>		

Table 7: Overview of the reasons for exclusion of the studies – indirect comparison: vildagliptin vs. glimepiride

Comparison Study	Reasons for exclusion			
	Population (type of prior treatment)	Intervention	ACT	Common comparator
Vildagliptin vs. gliclazide				
LAF237A2310	●	○	-	-
Glimepiride vs. gliclazide				
GUIDE study	●	-	○	○
Kaneko 1993	●	-	○	●
●: reason for exclusion; ○: uncertain; ACT: appropriate comparator therapy; vs.: versus				

According to the inclusion criteria of the study LAF237A2310, neither metformin intolerance nor a metformin contraindication was a prerequisite for enrolment of the patients. Instead, rescue treatment with metformin was envisaged in the study (from week 24). Hence the study was not conducted with the relevant patient population. This also applies to the 2 studies [6,7] on the comparison of glimepiride with gliclazide, of which the company included the subgroup results of the patients only pretreated with diet in the indirect comparison. The inclusion and exclusion criteria of these studies did not provide any information about whether the patients had metformin intolerance or contraindications (see also Section 2.9.2.2 of the full dossier assessment). The company did not provide any information on the approval compliance of the study population; it did also not prove the transferability of the results. Overall, the studies presented for the indirect comparison were therefore unsuitable to draw conclusions on the added benefit of the vildagliptin monotherapy versus the ACT.

Additional reasons should be pointed out that limit the usability of the studies:

- In the study LAF237A2310, a blood-glucose lowering substance was only used for titration in the gliclazide arm. Hence not only drugs, but treatment regimens with different treatment goals were compared in the study. This problem therefore also existed in the comparison of interest between vildagliptin and the ACT glimepiride using the indirect comparison.
- The target levels for the titration differed between the 3 studies, and it was therefore unclear whether the common comparator in the studies was sufficiently similar.
- Due to the considerably lower dosage of gliclazide, the common comparator of the study Kaneko 1993 could not be compared with the reference study LAF237A2310.

In summary, the indirect comparison presented by the company was unsuitable to draw conclusions on the added benefit of the monotherapy with vildagliptin versus the ACT.

Summary

Overall, no relevant data were available for assessing the added benefit versus the ACT, neither for a direct comparison nor for an indirect comparison.

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 2.9.2.4 and 2.9.2.4.1 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, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.9.2.4.1 and 2.9.2.4.2 of the full dossier assessment.

2.3.2 Results on added benefit

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

2.3.3 Extent and probability of added benefit

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

The company claimed that due to a lack of data it could not calculate a direct and not more than an only partial indirect comparison versus the ACT. It postulated that RCTs with other comparators showed an added benefit without providing any evidence for this conclusion, and rated this added benefit as "non-quantifiable".

2.4 Research question A2: combination of vildagliptin plus metformin

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 plus metformin (studies completed up to 19 February 2013)
- Bibliographical literature search on vildagliptin plus metformin (last search on 6 February 2013)
- Search in trial registries for studies on vildagliptin plus 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 the combination of vildagliptin plus metformin were identified from the steps of information retrieval mentioned. In contrast, the company included 4 direct comparative studies (LAF237A2308 [9], LAF237ADE06T [10], LAF237AFR03 [11] and Jeon 2011 [12]). However, all 4 studies were unsuitable for answering the research question.

Table 8 shows the characteristics of these 4 studies and Table 9 a description of the interventions. Table 10 summarizes the reasons for exclusion.

Table 8: Characteristics of the studies included by the company – RCT, direct comparison: combination of vildagliptin plus 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 phase of at least 2 weeks.	HbA1c > 7%

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

Table 9: Characteristics of the intervention of the studies included by the company – RCT, direct comparison: combination of vildagliptin plus metformin vs. sulfonylurea (glimepiride) plus metformin

Study	Intervention Number of patients	Comparator Number of patients
LAF237A2308	<ul style="list-style-type: none"> ▪ 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 	<ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ Vildagliptin 50 mg/metformin^a 1000 mg fixed combination (twice a day) ▪ N = 22 	<ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ Vildagliptin 50 mg (twice a day) + metformin at previous dosage ▪ N = 24 	<ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ Vildagliptin 50 mg (twice a day) + metformin 500 mg (twice a day) ▪ N = 51 	<ul style="list-style-type: none"> ▪ 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
<p>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).</p> <p>FPG: fasting plasma glucose; N: number of randomized patients; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus</p>		

Table 10: Overview of the reasons for exclusion of the studies – direct comparison: vildagliptin plus 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 [9] was unsuitable for answering the present research question for the following reasons:

- The administration of glimepiride did not comply with the recommendations provided in the SPC [13]. 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 \leq 100 mg/dl). Moreover, titration based on target blood glucose levels with a blood-glucose lowering drug was only performed in the glimepiride group, but not in the vildagliptin group. Hence the study LAF237A2308 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 \leq 7.2%. According to current knowledge, for a relevant proportion of the 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 [10] 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 (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 [11] 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 structural equality of the glimepiride group in comparison with the vildagliptin group was no longer guaranteed in this type of analysis, and the results could therefore no longer be interpreted.

The study Jeon 2011 [12] was unsuitable for answering the present research question for the following reasons:

- Both treatment-naïve 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-naïve 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 an initial dose of glimepiride of 4 mg a day at the start of the treatment. This does not comply with the approval (at least for those patients who were not pretreated with glimepiride) [13].

Summary

Overall, there were no studies that would have been suitable for assessing the added benefit of the combination of vildagliptin plus metformin versus the ACT "sulfonylurea plus metformin". Appendix A of the full dossier assessment contains an additional reporting of results on the study LAF237A2308 due to its size.

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 2.9.3.2 and 2.9.3.4.1 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, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.9.3.4 and 2.9.3.4.2 of the full dossier assessment.

2.4.2 Results on added benefit

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

2.4.3 Extent and probability of added benefit

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

This assessment deviates from that of the company, which derived a considerable added benefit (which could be "safely assumed", according to the company) of the combination of vildagliptin plus metformin.

2.5 Research question A3: combination of vildagliptin 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 plus sulfonylurea (studies completed up to 19 February 2013)
- Bibliographical literature search on vildagliptin plus sulfonylurea (last search on 6 February 2013)
- Search in trial registries for studies on vildagliptin plus sulfonylurea (last search on 5 February 2013)
- Study list on vildagliptin plus sulfonylurea for indirect comparisons (studies completed up to 16 November 2012)
- Bibliographical literature search on human insulin plus sulfonylurea (last search on 7 February 2013)
- Search in trial registries for studies on human insulin plus sulfonylurea (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 identified no direct comparative studies on the combination of vildagliptin plus sulfonylurea versus the ACT "human insulin plus sulfonylurea" chosen by the company. The company also identified no studies that were suitable for an indirect comparison.

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, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier.

2.5.2 Results on added benefit

There were no relevant data for the subindication of vildagliptin plus sulfonylurea. Hence the added benefit versus the ACT specified by the G-BA is not proven in this 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 the combination of vildagliptin plus sulfonylurea in comparison with the

ACT specified by the G-BA. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

The company claimed that due to a lack of data it could not calculate a direct and not more than an only partial indirect comparison versus the ACT. It postulated that RCTs with other comparators showed an added benefit without providing any evidence for this conclusion, and rated this added benefit as "non-quantifiable".

2.6 Research question A4: Combination of vildagliptin plus insulin (with or without metformin)

2.6.1 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 plus insulin (with or without metformin) (studies completed up to 19 February 2013)
- Bibliographical literature search on vildagliptin plus insulin (with or without metformin) (last search on 6 February 2013)
- Search in trial registries for studies on vildagliptin plus insulin (with or without metformin) (last search on 5 February 2013)
- Study list on vildagliptin plus insulin (with or without metformin) 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 approached its research question both via a direct comparison and via an indirect comparison:

- Direct comparison: combination of vildagliptin plus insulin with metformin versus human insulin plus metformin
- Indirect comparison: combination of vildagliptin plus insulin without metformin versus human insulin plus metformin

Direct comparison

No relevant studies suitable for assessing the added benefit of the combination of vildagliptin plus insulin (with or without metformin) 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 [14]) and analysed those

patients who received vildagliptin plus insulin with metformin or placebo plus insulin with metformin.

Table 11 shows the characteristics of the study LAF237A23135 and Table 12 a description of the intervention.

Table 11: Characteristics of the studies included by the company – RCT, direct comparison: vildagliptin plus insulin plus metformin 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 $\leq 11\%$

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

Table 12: Characteristics of the interventions – RCT, direct comparison: vildagliptin plus insulin plus metformin vs. human insulin plus metformin

Study	Intervention Number of patients	Comparator Number of patients
LAF237-A23135	<ul style="list-style-type: none"> ▪ Vildagliptin 50 mg twice a day + insulin ▪ \pm metformin at previous dosage (maintained stable) ▪ Total population: N= 228, thereof metformin subpopulation^a: n = 139 	<ul style="list-style-type: none"> ▪ Placebo twice a day + insulin ▪ \pm metformin at previous dosage (maintained stable) ▪ Total population: N= 221, thereof metformin subpopulation^a: n = 137
Treatment with insulin		
<ul style="list-style-type: none"> ▪ 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 both 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 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 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 plus insulin (with metformin) versus the ACT (human insulin with or without metformin). To draw conclusions on the added benefit, the administration of vildagliptin plus insulin (with metformin) would have to be compared with other optimization strategies such as optimizing insulin therapy including changing the type or regimen of the insulin.

Indirect comparison

The company conducted an adjusted indirect comparison of vildagliptin plus insulin versus insulin plus metformin. The company presented a total of 9 studies for this adjusted indirect comparison.

The company included the placebo-controlled study LAF237A23135, which it had also used for the direct comparison, for the comparison with vildagliptin. It only analysed the subpopulation of the study that received vildagliptin plus insulin without metformin to answer its research question versus human insulin plus metformin. It analysed those patients from the comparator group who only received insulin (without metformin) because this was to serve as the common comparator in the network presented (see Figure 1). On the chosen comparator therapy "insulin plus metformin", the company identified 8 studies, which were relevant from the company's point of view, for an indirect comparison (Civera 2008 [15], Vähätalo 2007 [16], Yilmaz 2007 [17], Ryysy 2001 [18], Mäkimattila 1999 [19], Aviles-Santa 1999 [20], Douek 2005 [21], Giugliano 1993 [22]).

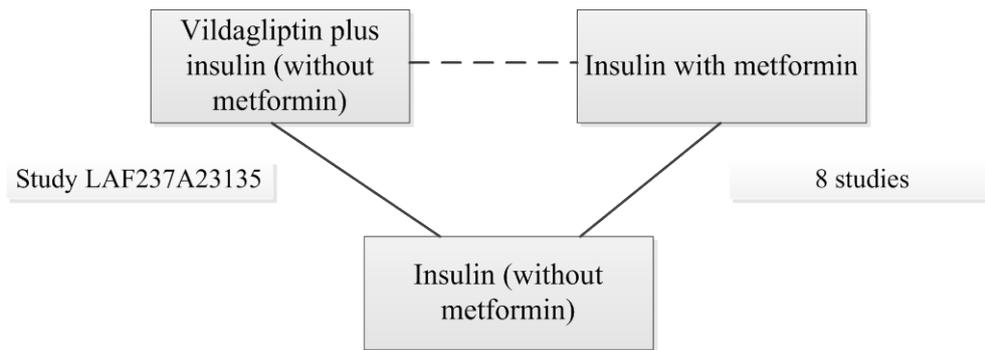


Figure 1: Network structure of the indirect comparison of vildagliptin plus insulin vs. insulin plus metformin presented in the dossier

All 8 studies on the comparator therapy were unsuitable for the indirect comparison. Table 13 shows the main characteristics of the studies and Table 14 a description of the interventions. Table 15 summarizes the reasons for exclusion.

Table 13: Characteristics of the studies on the comparator therapy included by the company – indirect comparison: vildagliptin plus insulin vs. insulin plus metformin

Comparison Study	Study design	Study duration	Population	
			Type of prior treatment	Criteria for inadequate glycaemic control
Metformin plus insulin vs. (placebo +) insulin				
Civera 2008	RCT, open-label, parallel	24 weeks	Adult patients with type 2 diabetes mellitus and with secondary treatment failure under combined OAD treatment	HbA1c > 8%
Vähätalo 2007	RCT, open-label, parallel	12 months	Adult patients with type 2 diabetes mellitus (duration > 5 years) with treatment failure under maximum OAD treatment and inadequate glycaemic control (for the first time of insulin therapy)	HbA1c > 7.5% and FPG > 144 mg/dl
Yilmaz 2007	Non-RCT, open-label, parallel	24 weeks	Adult patients with type 2 diabetes mellitus with inadequate glycaemic control under insulin monotherapy	HbA1c 7.0% to 14.5%
Ryysy 2001	RCT, partially blinded, parallel	52 weeks	Adult patients with type 2 diabetes mellitus with previous OAD treatment with glipizide or glyburide (exclusion criterion: previous insulin therapy for > 2 weeks)	FPG > 144 mg/dl
Mäkimmattila 1999	RCT, open-label, parallel	12 months	Adult patients with type 2 diabetes mellitus with previous OAD treatment with a maximum dosage of glipizide or glyburide and inadequate glycaemic control (exclusion criterion: previous insulin therapy for > 2 weeks)	FPG > 144 mg/dl
Avilés-Santa 1999	RCT, double-blind, parallel	24 weeks	Adult patients with type 2 diabetes mellitus with insulin therapy of ≥ 50 units a day for ≥ 2 years and inadequate glycaemic control	HbA1c $\geq 8.0\%$
Douek 2005	RCT, double-blind, parallel	12 months	Adult patients with type 2 diabetes mellitus with inadequate glycaemic control under maximum tolerated OAD treatment (mono-, dual or triple therapy) referred for switch to insulin	no data
Giugliano 1993	RCT, double-blind, parallel	24 weeks	Adult obese patients with type 2 diabetes mellitus with high-dose insulin therapy (mean daily dose 90 IU) after secondary treatment failure under maximum dosage of sulfonylureas and inadequate glycaemic control	no data
FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin; IU: international units; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus				

Table 14: Characteristics of the interventions – indirect comparison: vildagliptin plus insulin vs. insulin plus metformin

Comparison Study	Intervention Number of patients	Common comparator Number of patients
Metformin plus insulin vs. (placebo +) insulin		
Civera 2008	<ul style="list-style-type: none"> ▪ Metformin 850 mg twice a day (after breakfast and after evening meal) + NPH insulin once in the evening ▪ N = 12 	<ul style="list-style-type: none"> ▪ NPH insulin twice a day ▪ N = 13
Insulin dosage		
	<ul style="list-style-type: none"> ▪ Dosages were adjusted individually and at an endocrinologist's discretion at the study visits on the basis of blood glucose tests and the presence of hypoglycaemias (without specific algorithm). ▪ Adjustment or change of the insulin type or regimen was not envisaged. ▪ The key goal was to maintain a basal blood glucose of < 110 mg/dl. 	<ul style="list-style-type: none"> ▪ The key goal was to maintain a basal blood glucose of < 110 mg/dl and of < 120 mg/dl before the evening meal.
Vähätalo 2007	<ul style="list-style-type: none"> ▪ Metformin 2500 mg a day (or maximum tolerated dose) + NPH or lente insulin (in the evening) ▪ N = 26 	<ul style="list-style-type: none"> ▪ NPH or lente insulin twice a day ▪ N = 11
Insulin dosage		
	<ul style="list-style-type: none"> ▪ Insulin dose was adjusted individually at the study visits on the basis of fasting serum/plasma glucose and self-monitoring tests. ▪ Adjustment or change of the insulin type or regimen was not envisaged. 	
Yilmaz 2007	<ul style="list-style-type: none"> ▪ Metformin 1700 mg a day + insulin twice a day (mixed insulin with 30% of insulin aspart plus 70% of NPH insulin) ▪ N = 17 	<ul style="list-style-type: none"> ▪ Insulin twice a day (mixed insulin with 30% of insulin aspart plus 70% of NPH insulin) ▪ N = 19
Insulin dosage		
	<ul style="list-style-type: none"> ▪ Dosage was determined and adjusted individually at the study visits on the basis of fasting and postprandial glucose levels. ▪ Adjustment or change of the insulin type or regimen was not envisaged. 	
Ryysy 2001	<ul style="list-style-type: none"> ▪ Metformin 1000 mg twice a day (before breakfast and evening meal) + NPH insulin (in the evening) ▪ N = 17 	<ul style="list-style-type: none"> ▪ NPH insulin twice a day ▪ N = 23
Insulin dosage		
	<ul style="list-style-type: none"> ▪ Patients were trained to adjust the insulin dose themselves on the basis of home blood glucose tests (using recommended algorithm) ▪ Adjustment or change of the insulin type or regimen was not envisaged. 	

(continued on next page)

Table 14: Characteristics of the interventions – indirect comparison: vildagliptin plus insulin vs. insulin plus metformin (continuation)

Comparison Study	Intervention Number of patients	Common comparator Number of patients
Metformin plus insulin vs. (placebo +) insulin		
Mäkimattila 1999	<ul style="list-style-type: none"> ▪ Metformin 2000 mg a day + NPH insulin (in the evening) ▪ N = 13 	<ul style="list-style-type: none"> ▪ NPH insulin twice a day ▪ N = 13
Insulin dosage		
<ul style="list-style-type: none"> ▪ Adjustment of the insulin dosage based on the self-measurement of blood glucose (using recommended algorithm) ▪ Treatment goal: FPG < 108 mg/dl (HbA1c < 7.5%) ▪ Adjustment or change of the insulin type or regimen was not envisaged. 		
Avilés-Santa 1999	<ul style="list-style-type: none"> ▪ Metformin (maximum tolerated dose) + insulin ▪ N = 22 	<ul style="list-style-type: none"> ▪ Placebo + insulin ▪ N = 23
Insulin dosage		
<ul style="list-style-type: none"> ▪ All patients received at least 2 insulin injections a day; some patients received 70/30 insulin, others received intermediate-acting insulin twice a day in combination with 3 or 4 injections with short-acting insulin a day (baseline). ▪ Adjustment/change of the individual dosage in quantity, frequency and type of insulin at each study visit. Only the study staff adjusted the dose. ▪ Treatment goal: normoglycaemia (HbA1c ≤ 5.6 %) without severe hypoglycaemias. 		
Douek 2005	<ul style="list-style-type: none"> ▪ Metformin 1000 mg (or maximum tolerated dose) twice a day + insulin ▪ N = 92 	<ul style="list-style-type: none"> ▪ Placebo twice a day + insulin ▪ N = 91
Insulin dosage		
<ul style="list-style-type: none"> ▪ Patients received insulin therapy according to the local practice routine. No standard protocol was specified for adjusting the insulin. Consultation on individual dose adjustment at study visits and/or on telephone. ▪ Adjustment or change of the individual dosage, the type or regimen of insulin was possible. ▪ Target: blood glucose before the meal < 126 mg/dl without hypoglycaemia and with HbA1c < 7% 		
Giugliano 1993	<ul style="list-style-type: none"> ▪ Metformin 850 mg twice a day + insulin twice a day ▪ N = 27 	<ul style="list-style-type: none"> ▪ Placebo + insulin twice a day ▪ N = 23
Insulin dosage		
<ul style="list-style-type: none"> ▪ Increasing the dose was not allowed. The insulin dose could be reduced individually. ▪ Adjustment or change of the insulin type or regimen was not envisaged. 		
FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin; IU: international units; N: number of randomized patients; NPH: neutral protamine Hagedorn; vs.: versus		

Table 15: Overview of the reasons for exclusion of the studies on the ACT – indirect comparison: combination of vildagliptin plus insulin vs. insulin plus metformin

Study	Reasons for exclusion			
	Study design	Population (type of prior treatment)	ACT	Common comparator
Civera 2008		●	●	●
Vähätalo 2007		●	●	●
Yilmaz 2007	●		●	●
Ryysy 2001		●	●	●
Mäkimattila 1999		●	●	●
Aviles-Santa 1999				●
Douek 2005		●		●
Giugliano 1993			●	●
●: reason for exclusion; ACT: appropriate comparator therapy; vs.: versus				

The study LAF237A23135 constituted the link between the common comparator insulin (without metformin) and vildagliptin plus insulin. It can therefore be regarded as a reference study to assess the comparability of the common comparator between the studies. Based on this comparison, the respective common comparator insulin (with or without placebo) was not comparable with the reference study in all 8 studies that were included for the comparison with the ACT insulin plus metformin.

In the study LAF237A23135 [14], the prior treatment with insulin was to be continued unchanged, i.e. the type and frequency of insulin and the type of insulin therapy could not be changed, and the insulin dose had to remain stable (maximum dose increase of 10% compared with baseline). Further dose adjustments could only be performed in emergency situations, e.g. if symptoms of hyperglycaemia or repeated high FPG levels occurred. In all 8 studies (Civera 2008 [15], Vähätalo 2007 [16], Yilmaz 2007 [17], Ryysy 2001 [18], Mäkimattila 1999 [19], Aviles-Santa 1999 [20], Douek 2005 [21], Giugliano 1993 [22]), the insulin dose could be optimized for the individual patient in the treatment time. As the treatment that was to be considered as the common comparator was apparently different in the respective study arms, there was no common comparator for the indirect comparison presented that fulfilled the assumption of similarity [23]. Hence the indirect comparison was unadjusted. The result could therefore not be interpreted [1,24].

Furthermore, the studies were unsuitable for answering the research question for the following reasons:

- One of the 8 studies was not an RCT (Yilmaz 2007 [17]).
- In 5 studies, the wrong patient population was studied, i.e. no patients with stable insulin dose and inadequate glycaemic control (Civera 2008 [15], Vähätalo 2007 [16], Ryysy 2001 [18], Mäkimattila 1999 [19], Douek 2005 [21]).
- In 6 of the 8 studies, the type or regimen of the insulin could not be adjusted (Civera 2008 [15], Vähätalo 2007 [16], Yilmaz 2007 [17], Ryysy 2001 [18], Mäkimattila 1999 [19], Giugliano 1993 [22]).

Summary

Overall, no relevant data were available for assessing the added benefit of the combination of vildagliptin plus insulin (with or without metformin) versus the ACT, neither for a direct comparison nor for an indirect comparison.

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 2.9.5.4 and 2.9.5.4.1 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, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.9.5.4 and 2.9.5.4.2 of the full dossier assessment.

2.6.2 Results on added benefit

No relevant studies were available for the research question A4 on the combination of vildagliptin plus insulin (with or without metformin), neither for a direct comparison, nor for an indirect comparison. Hence the added benefit versus the ACT is not proven.

2.6.3 Extent and probability of added benefit

On the basis of the available data, there is no proof of an added benefit of the combination of vildagliptin plus insulin (with or without metformin) versus the ACT specified by the G-BA. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

This assessment deviates from that of the company, which derived a minor added benefit (which could be safely assumed) of the combination of vildagliptin plus insulin (with or without metformin).

2.7 Research question A5: combination of vildagliptin plus sulfonyleurea plus metformin

2.7.1 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 plus sulfonyleurea plus metformin (studies completed up to 19 February 2013)
- Bibliographical literature search on vildagliptin plus sulfonyleurea plus metformin (last search on 6 February 2013)
- Search in trial registries for studies on vildagliptin plus sulfonyleurea plus metformin (last search on 5 February 2013)
- Study list on vildagliptin plus sulfonyleurea plus metformin 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 identified no direct comparative studies on the combination of vildagliptin plus sulfonyleurea plus metformin versus the ACT "human insulin plus metformin" chosen by the company. The company also identified no studies that were suitable for an indirect comparison.

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, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier.

2.7.2 Results on added benefit

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

2.7.3 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 the combination of vildagliptin plus sulfonylurea plus metformin in comparison with the ACT specified by the G-BA. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

The company claimed that due to a lack of data it could not calculate a direct and not more than an only partial indirect comparison versus the ACT. It postulated that RCTs with other comparators showed an added benefit without providing any evidence for this conclusion, and rated this added benefit as "non-quantifiable".

2.8 Extent and probability of added benefit - summary

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

Table 16: Vildagliptin – extent and probability of added benefit

Research question	Subindication	ACT	Extent and probability of added benefit
A1	Monotherapy with vildagliptin	Sulfonylurea ^a	Added benefit not proven
A2	Vildagliptin plus metformin	Sulfonylurea ^a plus metformin	Added benefit not proven
A3	Vildagliptin plus sulfonylurea	Human insulin in combination with sulfonylurea ^a , if applicable only treatment with human insulin	Added benefit not proven
A4	Vildagliptin plus insulin (with or without metformin)	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
A5	Vildagliptin plus sulfonylurea plus metformin	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 2.9 of the full dossier assessment.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 4.0 [online]. 23 September 2011 [accessed: 18 June 2013]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to § 35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 05 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Novartis Pharma. Galvus: Fachinformation [online]. October 2012 [accessed: 08 April 2013]. URL: <http://www.fachinfo.de>.
4. Bundesministerium für Gesundheit. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage III: Übersicht der Verordnungseinschränkungen und -ausschlüsse; Glitazone zur Behandlung des Diabetes mellitus Typ 2 vom 17.06.2010. Bundesanzeiger 2010; 62(175): 3855.
5. Novartis. A multicenter, double-blind, randomized, active controlled study to compare the effect of long term treatment with LAF237 50 mg bid to gliclazide up to 320 mg daily in drug naive patients with type 2 diabetes: final analysis; study no LAF237A2310; full clinical study report [unpublished]. 2008.
6. Schernthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, Kvapil M et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest 2004; 34(8): 535-542.
7. Kaneko T, Kaku K, Sakamoto N, Hotta N, Nakagawa S, Goto Y et al. Clinical evaluation of glimepiride (HOE490) in non-insulin dependent diabetes mellitus: a double-blind comparative study versus gliclazide [Japanese]. Journal of Clinical Therapeutics and Medicines 1993; 9(5): 1145-1177.
8. Tessier D, Dawson K, Tetrault JP, Bravo G, Meneilly GS. Glibenclamide vs gliclazide in type 2 diabetes of the elderly. Diabet Med 1994; 11(10): 974-980.
9. Novartis. A multicenter, randomized, double-blind, active controlled study to compare the long-term effect of treatment with LAF237 50 mg bid to glimepiride up to 6 mg daily as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: study no LAF237A 2308; full clinical study report [unpublished]. 2008.
10. Ikfe Cro. Effect of adding vildagliptin on beta cell function and cardiovascular risk markers in patients with moderate metabolic control during metformin monotherapy: study CLAF237ADE06T; clinical study report [unpublished]. 2012.
11. Novartis. Prospective, randomised, open-label study comparing over 6 months the clinical benefit on hypoglycaemia of vildagliptin versus another oral antidiabetic drug as add-on therapy in elderly patients with type 2 diabetes insufficiently controlled with metformin alone: study CLAF237AFR03; clinical study report [unpublished]. 2012.
12. Jeon HJ, Oh TK. Comparison of vildagliptin-metformin and glimepiride-metformin treatments in type 2 diabetic patients. Diabetes Metab J 2011; 35(5): 529-535.
13. Sanofi Aventis. Amaryl: Fachinformation [online]. June 2011 [accessed: 30 October 2012]. URL: <http://www.fachinfo.de>.
14. Novartis. A 24-week, multi-center, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy and safety of vildagliptin 50mg bid as an add-on therapy to insulin, with or without metformin, in patients with type 2 diabetes mellitus: study no CLAF237A23135; full clinical study report [unpublished]. 2012.

15. Civera M, Merchante A, Salvador M, Sanz J, Martinez I. Safety and efficacy of repaglinide in combination with metformin and bedtime NPH insulin as an insulin treatment regimen in type 2 diabetes. *Diabetes Res Clin Pract* 2008; 79(1): 42-47.
16. Vähätalo M, Rönnemaa T, Viikari J. Recognition of fasting or overall hyperglycaemia when starting insulin treatment in patients with type 2 diabetes in general practice. *Scand J Prim Health Care* 2007; 25(3): 147-153.
17. Yilmaz H, Gursoy A, Sahin M, Guvener Demirag N. Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and rosiglitazone or insulin and acarbose in type 2 diabetes. *Acta Diabetol* 2007; 44(4): 187-192.
18. Ryysy L, Yki-Järvinen H. Improvement of glycemic control by 1 year of insulin therapy leads to a sustained decrease in sE-selectin concentrations in type 2 diabetes. *Diabetes Care* 2001; 24(3): 549-554.
19. Mäkimattila S, Nikkilä K, Yki-Järvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with type II diabetes mellitus. *Diabetologia* 1999; 42(4): 406-412.
20. Aviles-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999; 131(3): 182-188.
21. Douek IF, Allen SE, Ewings P, Gale EAM, Bingley PJ. Continuing metformin when starting insulin in patients with type 2 diabetes: a double-blind randomized placebo-controlled trial. *Diabet Med* 2005; 22(5): 634-640.
22. Giugliano D, Quatraro A, Consoli G, Minei A, Ceriello A, De Rosa N et al. Metformin for obese, insulin-treated diabetic patients: improvement in glycaemic control and reduction of metabolic risk factors. *Eur J Clin Pharmacol* 1993; 44(2): 107-112.
23. Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. *BMJ* 2009; 338: b1147.
24. Bender R, Schwenke C, Schmoor C, Hauschke D. Stellenwert von Ergebnissen aus indirekten Vergleichen: gemeinsame Stellungnahme von IQWiG, GMDS und IBS-DR [online]. 02 February 2012 [accessed: 10 May 2013]. URL: http://www.gmds.de/pdf/publikationen/stellungnahmen/120202_IQWIG_GMDS_IBS_DR.pdf.

The full report (German version) is published under
https://www.iqwig.de/de/projekte_ergebnisse/projekte/arszneimittelbewertung/a13_16_vildagliptin_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.3638.html.