IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A14-46

Vildagliptin – 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 – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2015). 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

Commissioning agency:
Federal Joint Committee

Commission awarded on:
3 December 2014

Internal Commission No.:
A14-46

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, Tübingen University, 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. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Daniel Fleer
- Andreas Gerber-Grote
- Ulrich Grouven
- Elke Hausner
- Petra Kohlepp
- Katrin Nink
- Volker Vervölgyi
- 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[3]

Page

[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BMI	body mass index
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IU	international units
NPH	neutral protamine Hagedorn
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to reassess the benefit of the drug vildagliptin. Because of new scientific findings, the pharmaceutical company (hereinafter referred to as "the company") had applied for this new benefit assessment for the following therapeutic indication: dual oral therapy of vildagliptin in combination with a sulfonylurea in patients with insufficient glycaemic control despite monotherapy with maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 3 December 2014.

Research question

The aim of the present report was the assessment of the added benefit of vildagliptin in dual oral therapy in combination with a sulfonylurea in comparison with the appropriate comparator therapy (ACT) in adult patients with type 2 diabetes mellitus with insufficient glycaemic control despite monotherapy with maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance.

For this therapeutic indication, the G-BA specified the following ACT:

- human insulin in combination with a sulfonylurea (glibenclamide, glimepiride), if applicable only treatment with human insulin

The company concurred with the G-BA's specification on the ACT and chose glimepiride as sulfonylurea.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA and was based on patient-relevant outcomes and on the evidence presented by the company in the dossier. A minimum study duration of 24 weeks was applicable.

Results

The company presented 1 study (LAF237ADE08 – BENEFIT) that directly compared vildagliptin with neutral protamine Hagedorn (NPH) insulin, each in addition to an ongoing glimepiride treatment.

The BENEFIT study was a randomized, active-controlled, open-label study sponsored by the company, which was conducted after the approval of vildagliptin. Adult patients with type 2 diabetes mellitus and contraindication or intolerance to metformin who had achieved no sufficient glycaemic control despite treatment with sulfonylurea during at least 12 weeks and who received the drug glimepiride at a stable dosage of 4 mg daily or, in case of intolerance,

at their maximum tolerated dose (up to a maximum of 4 mg). 162 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms with vildagliptin and NPH insulin, each in addition to their ongoing glimepiride treatment. The study duration was 24 weeks. Patient-relevant outcomes of the study were adverse events including hypoglycaemia. No outcomes on diabetic (micro- or macrovascular) late complications were recorded.

Comparison of different treatment regimens

After randomization, patients in the BENEFIT study received either 50 mg/day vildagliptin (fixed dosage) or NPH insulin. The insulin dose was increased based on the patients' fasting blood glucose levels after 2 or 4 weeks of treatment. The decision for dose increase at the visit was based on whether the highest fasting blood glucose level measured during the last 2 consecutive days was higher than 100 mg/dL. If this was the case, the insulin dose was increased by 2 to 8 international units (IU)/day depending on the measurement if no symptoms of hypoglycaemia and no fasting blood glucose level of 50 mg/dL or lower had occurred under the insulin dose last used. The dose could be reduced in severe or recurrent hypoglycaemia at the investigator's discretion.

It was clear that titration with a blood-glucose lowering drug aimed at a target blood glucose level was only conducted in the insulin arm, but not in the vildagliptin arm. Hence the BENEFIT study constituted a comparison of 2 treatment regimens (therapeutic strategy plus drug) and not of 2 drugs alone.

Adaptation of the insulin dosage was rigidly based on the specification of a near-normal target blood glucose level (fasting blood glucose ≤ 100 mg/dL) and it could not be inferred from the Appendix of the BENEFIT study that the physician had sufficient flexibility for an individual balancing of benefits and risks, also when normoglycaemia was aimed at. Due to the treatment regimen of titration based on target blood glucose levels used, the mean glycosylated haemoglobin A1c (HbA1c) value was lowered considerably more under NPH insulin than in the vildagliptin arm at both time points of recording (12 weeks and 24 weeks). The HbA1c mean difference [95% confidence interval] of the change in comparison with the baseline value between the 2 treatment arms was 0.27 [0.03; 0.51] after 12 weeks, and 0.32 [0.06; 0.58] after 24 weeks.

For this reason it is therefore uncertain that the effects observed in the study are in each case attributable to the drugs used. They may also have been caused solely by the different therapeutic strategies. This is particularly the case for the outcomes on hypoglycaemia because their occurrence depends on the HbA1c value.

In summary, the results of the BENEFIT study could not be interpreted in a meaningful way and were therefore unsuitable to derive an added benefit for the combination of vildagliptin with a sulfonylurea.

It should also be noted that no added benefit of vildagliptin could be derived even if the BENEFIT study was considered. There was no statistically significant difference between the treatment groups for any of the outcomes to be assessed as relevant.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug vildagliptin compared with the ACT is assessed as presented in Table 2:

Table 2: Vildagliptin – extent and probability of added benefit

Therapeutic indication[a]	**ACT**[b]	**Extent and probability of added benefit**
Treatment of type 2 diabetes mellitus in adults with dual oral therapy in combination with a sulfonylurea[c]	Human insulin in combination with a sulfonylurea (glibenclamide, **glimepiride**), if applicable only treatment with human insulin	Added benefit not proven
a: The present new benefit assessment because of new scientific findings only refers to this therapeutic indication. b: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. c: In patients with insufficient glycaemic control despite monotherapy with maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

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

2.2 Research question

The aim of the present report was the assessment of the added benefit of vildagliptin in dual oral therapy in combination with a sulfonylurea in comparison with the ACT in adult patients with type 2 diabetes mellitus with insufficient glycaemic control despite monotherapy with maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance.

For this therapeutic indication, the G-BA specified the following ACT:

- human insulin in combination with a sulfonylurea (glibenclamide, glimepiride), if applicable only treatment with human insulin

The company concurred with the G-BA's specification on the ACT and chose glimepiride as sulfonylurea.

The present benefit assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier. A minimum study duration of 24 weeks was applicable.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on vildagliptin (studies completed up to 15 November 2014)
- bibliographical literature search on vildagliptin (last search on 5 November 2014)
- search in trial registries for studies on vildagliptin (last search on 28 October 2014)

To check the completeness of the study pool:

- bibliographical literature search on vildagliptin (last search on 15 December 2014)
- search in trial registries for studies on vildagliptin (last search on 15 December 2014)

No relevant study was identified from the check.

From the steps of information retrieval mentioned, the company identified 1 direct comparative study (LAF237ADE08 – BENEFIT [4,5]), hereinafter referred to as "BENEFIT".

This study was unsuitable to derive conclusions on the added benefit of vildagliptin in the combination therapy with a sulfonylurea versus the ACT specified by the G-BA. This is justified below.

Study design of the BENEFIT study

Relevant information on the BENEFIT study is presented in Table 3 and Table 4.

Table 3: Characteristics of the studies included – RCT, direct comparison: vildagliptin + glimepiride vs. NPH insulin + glimepiride

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
LAF237ADE08 BENEFIT	RCT, open-label, parallel	Adult patients with type 2 diabetes mellitus, metformin contraindication or intolerance and insufficient glycaemic control (HbA1c ≥ 7.0% to ≤ 8.5%) under SU treatment	Each in combination with glimepiride: ▪ vildagliptin (N = 83)[b] ▪ NPH insulin (N = 79)	▪ Run-in phase: 1 week ▪ Treatment phase: 24 weeks	47 study centres in Germany 8/2012 – 10/2013	Primary: composite outcome (HbA1c, confirmed hypoglycaemia and body weight), confirmed hypoglycaemia Secondary: adverse events, hypoglycaemia

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: 82 patients are contained in the total study population underlying the analysis (FAS). One patient was randomized but died before the start of treatment and was not included in the analyses.

FAS: full analysis set; HbA1c: glycosylated haemoglobin A1c; N: number of randomized patients; NPH: neutral protamine Hagedorn; RCT: randomized controlled trial; SU: sulfonylurea; vs.: versus

Table 4: Characteristics of the interventions – RCT, direct comparison: vildagliptin + glimepiride vs. NPH insulin + glimepiride

Study	Intervention	Comparison
LAF237ADE08 BENEFIT	Vildagliptin 50 mg, orally, once daily + glimepiride 4 mg, once daily[a] (or maximum tolerated dose up to 4 mg)	NPH insulin, subcutaneously, once daily + glimepiride 4 mg, once daily[a] (or maximum tolerated dose up to 4 mg) <u>Insulin dosage</u> *Titration, dose increase:* ▪ starting dose[b]: 0.3 – 0.4 IU/kg body weight/day ▪ titration based on target value on the basis of fasting blood glucose according to the following regimen for dose increase[c]: ▫ > 100 mg/dL – ≤ 120 mg/dL: 2 IU/day ▫ > 120 mg/dL – ≤ 140 mg/dL: 4 IU/day ▫ > 140 mg/dL – ≤ 160 mg/dL: 6 IU/day ▫ > 160 mg/dL: 8 IU/day *Basis of decision for dose increase[d]:* ▪ highest fasting blood glucose level > 100 mg/dL (> 5.5 mmol/L) ▪ no symptoms of hypoglycaemia or fasting blood glucose level ≤ 50 mg/dL under the last dose of insulin *Dose reduction and discontinuation of medication:* ▪ dose could be reduced in severe or recurrent hypoglycaemia at the investigator's discretion ▪ discontinuation of study medication in case of severe or recurrent hypoglycaemia (i.e.: 2 unexplained hypoglycaemias requiring third-party assistance or > 3 symptomatic hypoglycaemias/week)
	Pretreatment: ▪ no antidiabetics except sulfonylurea were allowed 12 weeks before randomization ▪ sulfonylurea for at least 12 weeks before the start of the study, thereof glimepiride for at least 4 weeks before visit 1 in the maximum tolerated dose (up to 4 mg) in a stable dosage	

a: The glimepiride dosage was to be maintained unchanged during the entire study.
b: Starting dose based on the BMI: administration of 0.3 IU/kg in BMI < 25 kg/m², and 0.4 IU/kg in BMI ≥ 25 kg/m².
c: Dose increase after 2 and 4 weeks of treatment, subsequent frequency of dose adjustments was at the investigator's discretion.
d: Fasting blood glucose levels based on patients' self-measurements within the last 2 consecutive days.
BMI: body mass index; IU: international units; NPH: neutral protamine Hagedorn; RCT: randomized controlled trial; vs.: versus

The BENEFIT study was a randomized, active-controlled, open-label study sponsored by the company, which was conducted after the approval of vildagliptin. According to the company, the study was planned specifically for the benefit assessment according to § 35a SGB V and conducted in Germany. Adult patients with type 2 diabetes mellitus and contraindication or intolerance to metformin who had achieved no sufficient glycaemic control despite treatment

with sulfonylurea during at least 12 weeks (HbA1c at the first visit ≥ 7.0% and ≤ 8.5%). Moreover, the sulfonylurea had to be the drug glimepiride in a stable dosage of 4 mg daily or, in case of intolerance, in the maximum tolerated dose (up to 4 mg maximum), for at least 4 weeks before visit 1.

The study comprised a run-in phase of 1 week and a treatment phase of 24 weeks. All patients had to maintain their respective glimepiride dose unchanged during the entire study duration (further antidiabetics were not allowed).

162 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms with vildagliptin and NPH insulin, each in addition to their ongoing glimepiride treatment.

Patient-relevant outcomes of the study were adverse events including hypoglycaemia. No outcomes on diabetic (micro- or macrovascular) late complications were recorded.

Comparison of different treatment regimens

After randomization, patients in the BENEFIT study received either 50 mg/day vildagliptin (fixed dosage) or NPH insulin (planned titration depending on the fasting blood glucose level). The starting dose in the NPH insulin arm was 0.3 to 0.4 IU/kg body weight/day depending on the body mass index (BMI). Dose increases were planned after 2 and 4 weeks of treatment, subsequent frequency of dose adjustments was at the investigator's discretion. The decision for dose increase at the visit was based on whether the highest fasting blood glucose level measured during the last 2 consecutive days was higher than 100 mg/dL. If this was the case, the insulin dose was increased by 2 to 8 IU/day depending on the measurement if no symptoms of hypoglycaemia and no fasting blood glucose level of 50 mg/dL or lower had occurred under the insulin dose last used. The dose could be reduced in severe or recurrent hypoglycaemia at the investigator's discretion.

It was clear that titration with a blood-glucose lowering drug aimed at a target blood glucose level was only conducted in the insulin arm, but not in the vildagliptin arm. Hence the BENEFIT study constituted a comparison of 2 treatment regimens (therapeutic strategy plus drug) and not of 2 drugs alone. It is therefore uncertain whether the effects observed in the study are solely attributable to the respective drugs used.

Adaptation of the insulin dosage was rigidly based on the specification of a near-normal target blood glucose level (fasting blood glucose ≤ 100 mg/dL) and it could not be inferred from the Appendix of the BENEFIT study that the physician had sufficient flexibility for an individual balancing of benefits and risks, also when normoglycaemia was aimed at.

Figure 1 shows the change in HbA1c value in the target population of the BENEFIT study in comparison with the baseline value and illustrates the effect of the different treatment regimens in the study arms.

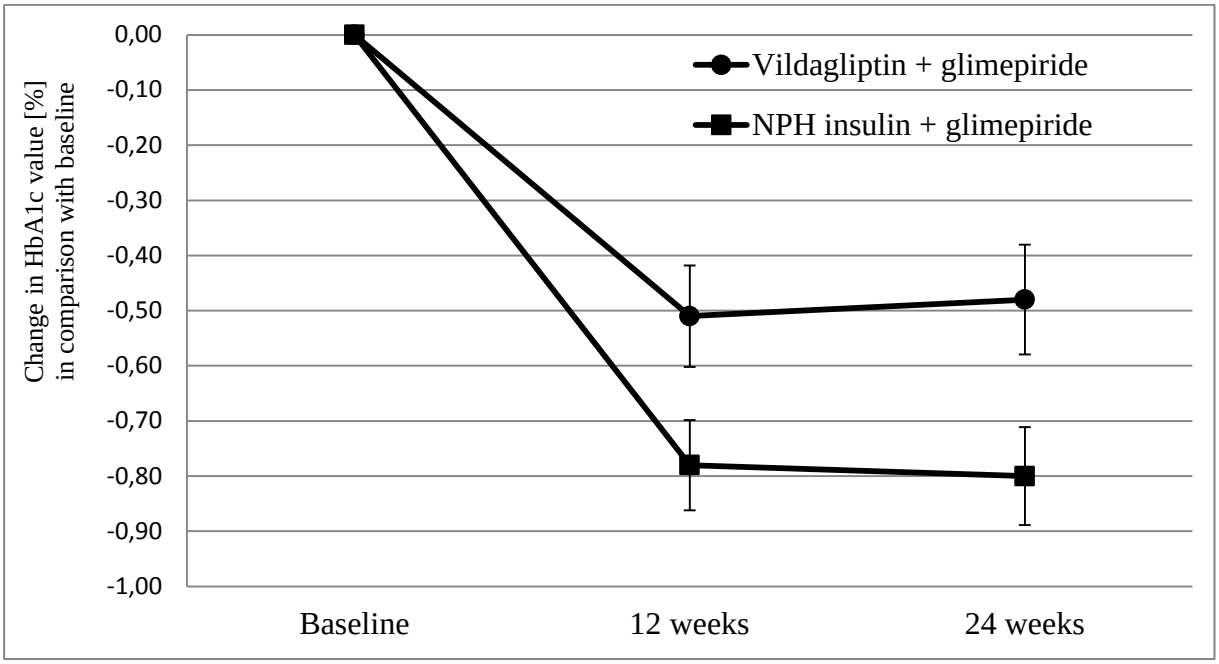

Figure 1: Change in HbA1c value in comparison with baseline in the BENEFIT study (mean ± standard error)

Due to the treatment regimen of titration based on target blood glucose levels used, the mean HbA1c value was lowered considerably more under NPH insulin than in the vildagliptin arm at both time points of recording (12 weeks and 24 weeks). The HbA1c mean difference [95% confidence interval] of the change in comparison with the baseline value between the 2 treatment arms was 0.27 [0.03; 0.51] after 12 weeks, and 0.32 [0.06; 0.58] after 24 weeks[5].

For this reason it is therefore uncertain that the effects observed in the study are in each case attributable to the drugs used. They may also have been caused solely by the different therapeutic strategies. This is particularly the case for the outcomes on hypoglycaemia because their occurrence depends on the HbA1c value. The BENEFIT study was therefore unsuitable to derive an added benefit for the combination of vildagliptin with a sulfonylurea.

The company's rationale that the observed differences in HbA1c were statistically significant, but below the threshold of 0.3 percentage points considered to be clinically relevant according to the European Medicines Agency (EMA) [6], was not followed. A difference in the sense of equivalence testing is only to be regarded irrelevant when the total confidence interval of the group difference is within the irrelevance range of ± 0.3 percentage points. However, this was not the case, as can be seen in the confidence intervals presented above. Irrespective of the question whether this threshold is considered to be relevant for the present benefit assessment, this prerequisite was therefore not fulfilled in the BENEFIT study.

[5] Institute's calculation based on available information. In Module 4, the company presented an adjusted value, which was not envisaged in the study plan, for the 24-week time point, which only deviated slightly, however: 0.29 [0.04; 0.55] percentage points.

Insulin dose

Against the background of the observed clear differences in the changes of the HbA1c value in both study arms and during the total course of the study, the mean insulin dose applied at the end of the study then was of no importance. This was rated as low by the company. The company additionally claimed that, according the study protocol, the titration over the total course of the study was explicitly conducted in accordance with the objective to avoid hypoglycaemia. The company additionally presented analyses for hypoglycaemic events for week 5 and later to show that the effect remained stable also under exclusion of the starting phase. However, these arguments played no role in so far as the difference in the course of HbA1c between the treatment arms was evident over the total course of the study duration and hence the interpretation of the study results – particularly regarding hypoglycaemia – was not possible, also not using the analyses for week 5 and later presented. The investigators could increase the dose of insulin over the total course of the study, also after week 4. The fact that the insulin dose was increased in 71% of the study participants in the insulin arm at least once in the course of the study also showed that the different therapeutic strategies were also implemented in the study.

Suitability of the target blood glucose level for the patients included

As already described, there was no individual balancing of benefits and risks regarding the target blood glucose level. However, for a large proportion of patients in the study, the near-normal fasting blood glucose level specified in the study might not be the optimum treatment goal. 60% of the patients in the BENEFIT study were 65 years and older, for example. At the same time, half of the participants had a baseline HbA1c value of 7.60% maximum.

Hence the company additionally presented results of the subpopulation of patients with baseline HbA1c $\geq$ 7.5%, which, from the company's point of view, are to be principally regarded as requiring treatment due to the blood glucose target range of the National Care Guideline [7]. Irrespective of whether this rationale is followed, there was a marked difference in the change of the mean HbA1c value between the study arms also for this subpopulation, which was even more pronounced than in the total population: 0.33 percentage points after 12 weeks and 0.38 percentage points after 24 weeks[6]. Hence like the analysis of the total study population, this analysis is also to be considered unsuitable for the benefit assessment.

Conclusions

Overall, the BENEFIT study was a comparison of 2 treatment regimens (therapeutic strategy plus drug) and not of 2 drugs alone. The observed decrease in mean HbA1c value, which was markedly more pronounced in the insulin group, is associated with a higher risk of hypoglycaemia, and an associated influence on the observed rate of hypoglycaemia under

[6] Institute's calculation based on available information. In Module 4, the company presented an adjusted value, which was not envisaged in the study plan, for the 24-week time point, which only deviated slightly, however: 0.36 [-0.01; 0.72] percentage points.

insulin in comparison with the vildagliptin group cannot be excluded. Hence the substance-specific effect particularly on hypoglycaemia remains unclear.

Overall, the results of BENEFIT study cannot be interpreted in a meaningful way because of the different treatment regimens.

It should also be noted that no added benefit of vildagliptin could be derived even if the BENEFIT study was considered. The corresponding results are presented as additional information in Appendix A of the full dossier assessment. There was no statistically significant difference between the treatment groups for any of the outcomes to be assessed as relevant.

2.4 Results on added benefit

No relevant data were available for assessing the added benefit of vildagliptin in combination with a sulfonylurea. Hence the added benefit of vildagliptin in combination with a sulfonylurea versus the ACT is not proven.

This deviates from the company's assessment, which derived an added benefit based on the results of the BENEFIT study presented.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of vildagliptin in combination with a sulfonylurea versus the ACT is shown in Table 5.

Table 5: Vildagliptin – extent and probability of added benefit

Therapeutic indication[a]	**ACT**[b]	**Extent and probability of added benefit**
Treatment of type 2 diabetes mellitus in adults with dual oral therapy in combination with a sulfonylurea[c]	Human insulin in combination with a sulfonylurea (glibenclamide, **glimepiride**), if applicable only treatment with human insulin	Added benefit not proven
a: The present new benefit assessment because of new scientific findings only refers to this therapeutic indication. b: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. c: In patients with insufficient glycaemic control despite monotherapy with maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

This assessment deviates from that of the company, which derived an indication of a considerable added benefit of vildagliptin in combination with a sulfonylurea.

2.6 List of included studies

Not applicable as no studies were included in the benefit 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 4.1 [online]. 28 November 2013 [accessed: 1 August 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.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: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Gemeinsamer Bundesausschuss. Verfahrensordnung des Gemeinsamen Bundesausschusses [online]. 19 November 2014 [accessed: 8 December 2014]. URL: https://www.g-ba.de/downloads/62-492-938/VerfO_2014-06-19_iK-2014-11-19.pdf.

4. Novartis Pharmaceuticals. Safety and efficacy of vildagliptin versus NPH insulin add-on to glimepiride in type 2 diabetes mellitus patients: full text view [online]. In: ClinicalTrials.gov. 28 October 2013 [accessed: 21 January 2015]. URL: http://ClinicalTrials.gov/show/NCT01649466.

5. Novartis Pharma. A randomized open-label study to compare safety and efficacy of vildagliptin versus NPH insulin add-on to glimepiride in patients with type 2 diabetes mellitus that do not reach adequate glycemic control on their current sulfonylurea monotherapy [online]. In: EU Clinical Trials Register. [Accessed: 21 January 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-001143-46.

6. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus [online]. 14 May 2012 [accessed: 23 January 2015]. URL: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129256.

7. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes: Langfassung; Version 4 [online]. November 2014 [accessed: 17 December 2014]. URL: http://www.leitlinien.de/mdb/downloads/nvl/diabetes-mellitus/dm-therapie-1aufl-vers4-lang.pdf.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-46-vildagliptin-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6510.html.