IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports - Commission No. A11-19

Linagliptin –

Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Linagliptin – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 28.12.2011). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding

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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.

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Keywords: linagliptin; diabetes mellitus, type 2; benefit assessment

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

List of abbreviations

Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)

2. Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In its letter of 05.10.2011, the Federal Joint Committee (G-BA) commissioned IQWiG to perform a benefit assessment of the drug linagliptin in accordance with § 35a Social Code Book (SGB) V. This assessment was performed on the basis of a dossier of the pharmaceutical company. The dossier was sent to IQWiG with the letter of 05.10.2011.

Research question

The benefit assessment of linagliptin was performed for the following therapeutic indication: "treatment of type 2 diabetes mellitus to improve glycaemic control in adults" [1]:

The benefit assessment was performed on the basis of the following comparisons:

- A sulfonylurea (glibenclamide, glimepiride) versus monotherapy with linagliptin, "in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment" [1].
- A sulfonylurea (glibenclamide, glimepiride) + metformin versus dual combination therapy with linagliptin and metformin, "when diet and exercise plus metformin alone do not provide adequate glycaemic control" [1].
- Metformin + human insulin versus triple combination therapy with linagliptin + a sulfonylurea + metformin, "when diet and exercise plus dual therapy with these medicinal products [a sulfonylurea + metformin] do not provide adequate glycaemic control" [1].

The dossier from the pharmaceutical company is inconsistent with this, in that it compares linagliptin with sitagliptin in all 3 patients groups. Thus it deviates from the G-BA's specification, without providing adequate justification for this deviation.

Results

In its dossier, the pharmaceutical company performed no assessment of the research questions listed above, as it selected another comparator therapy. Studies relevant to the above research questions were explicitly excluded from the assessment by the pharmaceutical company. Thus, the assessment presented by the pharmaceutical company in the dossier provides no proof of added benefit from linagliptin in comparison to the appropriate comparator therapy specified by the G-BA. This applies to all 3 research questions given above – monotherapy, dual combination therapy and triple combination therapy.

Probability and extent of added benefit, patient groups with therapeutically relevant added benefit

On the basis of the presented results, the extent and probability of the added benefit of the drug linagliptin was assessed as follows:

- There is no proof of added benefit.

The result is as follows for patient groups with therapeutically relevant added benefit:

- There are no patient groups for which therapeutically relevant added benefit has been proven.

The G-BA decides about added benefit.

2.2 Research question

The benefit assessment for linagliptin was performed for the following therapeutic indication: "treatment of type 2 diabetes mellitus to improve glycaemic control in adults" [1].

Linagliptin is approved for monotherapy and for dual and triple combination therapies. More details can be found in Table 1.

Table 1: Conditions of approval of linagliptin as monotherapy and combination therapy [1]

Monotherapy Linagliptin	"in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment"
Dual therapy Linagliptin + metformin	"when diet and exercise plus metformin alone do not provide adequate glycaemic control"
Triple therapy Linagliptin + a sulfonylurea + metformin	"when diet and exercise plus dual therapy with these medicinal products [a sulfonylurea + metformin] do not provide adequate glycaemic control"

In the dossier, the pharmaceutical company specifies sitagliptin as the appropriate comparator therapy for monotherapy, as well as for dual and triple combination therapies. This is inconsistent with the G-BA's specification of a sulfonylurea for the monotherapy and the dual combination therapy, and insulin for the triple combination therapy. Table 2 presents detailed information on the appropriate comparator therapies specified by the G-BA and the pharmaceutical company.

Table 2: Overview of the appropriate comparator therapies specified by the G-BA and the pharmaceutical company

	Appropriate comparator therapy of the G-BA	**Appropriate comparator therapy of the pharmaceutical company**
Monotherapy Linagliptin	a sulfonylurea[a]	sitagliptin
Dual combination therapy Linagliptin + metformin	a sulfonylurea[a] + metformin	sitagliptin + metformin
Triple combination therapy Linagliptin + a sulfonylurea + metformin	human insulin + metformin	sitagliptin + a sulfonylurea + metformin
a: Glibenclamide, glimepiride		

In the opinion of the Institute, the pharmaceutical company has provided inadequate justification for this deviation. Please refer to Section 2.7.1 of the full dossier assessment for a detailed explanation of this point.

The appropriate comparator therapy specified by the G-BA was used for the benefit assessment of linagliptin in the present dossier assessment.

The assessment was based on patient-relevant outcomes.

Additional information on the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier, as well as in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study list of the pharmaceutical company was used for the study pool.

The study list of the pharmaceutical company for linagliptin is based on the pharmaceutical company's approval studies and other studies sponsored by the pharmaceutical company, together with a bibliographic literature search and a search in trial registries for directly comparative studies with linagliptin or studies on the indirect comparison with sitagliptin. The information retrieval performed by the pharmaceutical company was in general not related to the appropriate comparator therapy specified by the G-BA. The study list included one relevant study with linagliptin in comparison to the appropriate comparator therapy as specified by the G-BA (Study 1218.20 on dual combination therapy). The pharmaceutical company explicitly excludes this study from its assessment, as the comparator therapy (glimepiride) was not the same as the comparator therapy that it had specified (sitagliptin).

Additional information on information retrieval and on the study pool for the present benefit assessment can be found in Module 4 Sections 4.2.2 and 4.2.3 of the dossier and in Section 2.7.2.3 of the full dossier assessment.

2.4 Results concerning added benefit

In its dossier, the pharmaceutical company performed no assessment of the research questions listed above, as it selected another comparator therapy. Studies relevant to the above research questions were explicitly excluded from the assessment by the pharmaceutical company. Thus, the assessment presented by the pharmaceutical company in the dossier provides no proof of added benefit from linagliptin in comparison to the appropriate comparator therapy specified by the G-BA. This applies to all 3 research questions given above – monotherapy, dual combination therapy and triple combination therapy.

Additional information on the results on the added benefit can be found in Module 4 Sections 4.3.1.3 and 4.3.2.1.3 of the dossier.

2.5 Extent and probability of the added benefit

The pharmaceutical company makes no statement on the extent and probability of added benefit in comparison to the appropriate comparator therapy as specified by the G-BA. In the dossier, the pharmaceutical company establishes no added benefit for linagliptin in comparison to the comparator therapy (sitagliptin) they had themselves selected. Additional information can be found in Section 2.7.2.5.2 of the full dossier assessment.

Overall, there is no proof of added benefit from linagliptin. Thus, there are also no patient groups for which therapeutically relevant added benefit can be deduced.

Additional information on the extent and probability of added benefit can be found in Module 4 Section 4.4 of the dossier and in Section 2.7.2.4 of the full dossier assessment.

2.6 List of included studies

The pharmaceutical company did not include any relevant study in its assessment for comparison with the appropriate comparator therapy specified by the G-BA.

References for English extract (please see full dossier assessment for full reference list)

1) European Medicines Agency. Product information 24/08/2011. Trajenta - EMEA/H/C/002110. Annex I - Summary of Product Characteristics. (Accessed on 18.04.2012). URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002110/WC500115745.pdf

The full report (German version) is published under www.iqwig.de.