IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Empagliflozin/metformin (type 2 diabetes mellitus) –

Addendum to Commission A16-13[1]

Addendum

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

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List of abbreviations

Abbreviation	Meaning
CSR	clinical study report
eGFR	estimated glomerular filtration rate
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)

1 Background

On 11 July 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-13 (Empagliflozin/metformin – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In Module 4 A [2] of its dossier on empagliflozin/metformin, the pharmaceutical company (hereinafter referred to as "the company") presented a study of direct comparison and 2 indirect comparisons for research question A (empagliflozin/metformin in comparison with metformin plus sulfonylurea). All studies used for this were already known from the first assessment A14-26 [3]. The data presented by the company were incomplete, however. In addition, there were noticeable discrepancies between the company's analyses in Module 4 A and the corresponding clinical study reports (CSRs).

Furthermore, the company had presented the study EMPA-REG-Outcome (hereinafter abbreviated as "EMPA-REG") in Module 4 C of its dossier [4]. This study was comprehensively assessed in dossier assessment A16-12 with the result that it was unsuitable for the benefit assessment. On the one hand, the company had presented no analyses that would have allowed a comparison with the appropriate comparator therapy. On the other, there were substantial deviations between the conduct of the study and the "standard treatment" mandated in the study protocol so that the results of the study were not interpretable.

With its written comments [5] and after the oral hearing [6], the company subsequently submitted data on the studies mentioned above. The G-BA commissioned IQWiG to assess study 1245.28, the indirect comparison under consideration of the studies 1245.28, 1275.1 and 1245.23/1245.31, and of the EMPA-REG study.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Research question A: empagliflozin/metformin

Study of direct comparison 1245.28

A detailed description of study 1245.28, its limitations, as well as tables presenting the study characteristics, the interventions and the study population can be found in the first benefit assessment of empagliflozin [3].

In its dossier on empagliflozin/metformin [2], the company presented results of study 1245.28 on the subpopulation of patients who received a daily dose of at least 1700 mg metformin. This corresponded to the relevant subpopulation for the assessment of empagliflozin/ metformin. It comprised about 70% of the total study population. In its dossier, the company did not present results on several patient-relevant outcomes, however, although it was already known from the first dossier assessment of empagliflozin [3], from the corresponding addendum [7] and from the G-BA's decision [8] which outcomes were relevant for the benefit assessment.

The company also did not subsequently submit the missing data with its written comments [5]. This aspect was also comprehensively discussed in the oral hearing of the current procedure [9]. The company then subsequently submitted data again [6]. These referred only to the single agent empagliflozin, however.

The underlying data for the fixed combination empagliflozin/metformin are therefore still incomplete; particularly analyses on relevant specific adverse events are still missing (see dossier assessment A16-13 [1]).

Furthermore, dossier assessment A16-13 described that there were unresolvable discrepancies between the information provided in the CSR and the additional analyses for the relevant subpopulation. For example, the CSR of study 1245.28 at 208 weeks [10] stated 104 events in the comparator arm for the outcome "symptomatic hypoglycaemia" (54 mg/dL ≤ plasma glucose ≤ 70 mg/dL) for the total population. In the additional analyses of study 1245.28 at 208 weeks [11], in contrast, more events (122) were mentioned for the relevant subpopulation although the subpopulation only constituted 70% of the total population. Due to the implausibility of the data, this raised general doubts about the additional analyses for the fixed combination empagliflozin/metformin. The company did not resolve these discrepancies, neither with the comment, nor with the data subsequently submitted after the oral hearing.

Overall, neither plausible nor complete analyses on study 1245.28 were available for the relevant subpopulation.

Indirect comparison

Analogously, the aspects mentioned above for study 1245.28 also apply to the indirect comparison of empagliflozin (10 mg)/metformin versus glimepiride using the common comparator empagliflozin 25 mg with the studies 1245.28, 1275.1 and 1245.23/1245.31.

The company correctly only considered the relevant subpopulation of the patients who received a daily dose of at least 1700 mg metformin in its dossier. However, these analyses were incomplete. In addition, the analyses on the relevant subpopulation conducted by the company were partly implausible [1].

Also regarding the indirect comparison, the company subsequently submitted no analyses on the relevant subpopulation in its comment [5] or in the data subsequently submitted after the oral hearing [6].

Overall, neither plausible nor complete analyses were available for the relevant subpopulation also for the indirect comparison of empagliflozin/metformin.

2.2 Study EMPA-REG

The EMPA-REG study was already comprehensively assessed in dossier assessment A16-12. The assessment concluded that, on the basis of the information provided in the company's dossier, the EMPA-REG study was unsuitable for a comparison with the G-BA's appropriate comparator therapy or for a comparison with "standard treatment". This was irrespective of the question whether it was about empagliflozin monotherapy or empagliflozin as component of the fixed combination with metformin. The relevant aspects and further analyses on this are summarized in Addendum A16-46 on the single agent empagliflozin, which is published at the same time as the present addendum [12].

In contrast to the single agent (see Addendum A16-46), the results of the EMPA-REG study cannot be presented for the fixed combination empagliflozin/metformin because the company conducted its assessment on the basis of the total population and not on the basis of the relevant subpopulation (combination with metformin in a daily dose of at least 1700 mg) [4]. On the one hand, this is inconsistent with the other approach of the company in the dossier (see also Section 2.1). On the other, it is inadequate because the relevant subpopulation comprised only about 66% of the EMPA-REG study and the company did not prove that the results of the total population can be transferred to the relevant subpopulation.

The company argued in its dossier that there was no proof of heterogeneity for the characteristic "metformin dose of at least 1700 mg daily". It concluded from this that there was transferability of the results of the total population to the relevant subpopulation. Irrespective of the question whether a negative interaction test alone is sufficient to assume transferability of the results, the analyses conducted by the company were incorrect because the company did not conduct the interaction test for the total population, but for the subgroup of patients treated with metformin. Specifically, the company did not investigate the

transferability of the results of the total population to the relevant subpopulation, but the transferability of the results of a subgroup (i.e. of all patients treated with metformin) to the relevant subpopulation (of the patients treated with metformin 1700 mg), but nonetheless subsequently analysed the total population. This approach is self-contradictory and unsuitable for the assessment of the fixed combination empagliflozin/metformin.

Furthermore, the company did not consider the restriction of approval in impaired renal function (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) also for the fixed combination. In addition, restriction of approval also exists for metformin in impaired renal function (eGFR < 45 mL/min/1.73 m^2). The proportion of the patients who were not treated in compliance with the approval in the relevant subpopulation was unclear because the company provided no information on this.

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