IQWiG Reports – Commission No. A21-148

Empagliflozin (heart failure) –

Addendum to Commission A21-93[1]

Addendum

Commission: A21-148
Version: 1.0
Status: 10 December 2021

[1] Translation of addendum A21-148 *Empagliflozin (Herzinsuffizienz) – Addendum zum Auftrag A21-93* (Version 1.0; Status: 10 December 2021. Please note: This document was translated by an external translator and 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
Empagliflozin (heart failure) – Addendum to Commission A21-93

Commissioning agency
Federal Joint Committee

Commission awarded on
23 November 2021

Internal Commission No.
A21-148

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Keywords: Empagliflozin, Heart Failure, Benefit Assessment, NCT03057977

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
HF	heart failure
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)

1 Background

On 23 November 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-93 (Empagliflozin – benefit assessment according to §35a Social Code Book V) [1].

For the assessment of the added benefit of empagliflozin in comparison with optimized standard therapy as the appropriate comparator therapy (ACT) in patients with symptomatic chronic heart failure (HF) with reduced ejection fraction, the dossier of the pharmaceutical company (hereinafter referred to as the "company") presented the study 1245.121 (hereinafter referred to as "EMPEROR-Reduced") [2] . No usable data on renal morbidity were available for the benefit assessment. The combined outcome on renal morbidity presented in the company's dossier comprises the components of chronic dialysis, kidney transplant, sustained reduction of estimated glomerular filtration rate (eGFR) by ≥ 40%, sustained eGFR < 15 mL/min/1.73 m² (for patients with a baseline eGFR ≥ 30 mL/min/1.73 m²) or sustained eGFR < 10 mL/min/1.73 m² (for patients with a baseline eGFR < 30 mL/min/1.73 m²). In the above operationalization, however, this outcome cannot be used for the benefit assessment since the component of eGFR reduction by ≥ 40% is not necessarily patient relevant and its severity is therefore not comparable to that of the remaining components of this composite outcome.

With its comments [3], the company submitted data on a composite renal morbidity outcome using a modified operationalization.

The G-BA commissioned IQWiG with assessing these additional data on the composite renal outcome as submitted by the company in the commenting procedure.

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

2 Assessment

2.1 Composite outcome on renal morbidity

The company's dossier presents results regarding a composite renal morbidity outcome which comprises the components of chronic dialysis, kidney transplant, sustained eGFR reduction by ≥ 40%, sustained eGFR < 15 mL/min/1.73 m² (for patients with a baseline eGFR ≥ 30 mL/min/1.73 m²) or sustained eGFR < 10 mL/min/1.73 m² (for patients with a baseline eGFR < 30 mL/min/1.73 m²). For a composite outcome to be eligible for inclusion in a benefit assessment, the individual components of the outcome must be both patient relevant and of similar severity. However, given the high baseline eGFR levels in the EMPEROR-Reduced study, the component of relative eGFR reduction by ≥ 40% is not necessarily patient-relevant and its severity is therefore not comparable to that of the remaining components of this composite outcome. Dossier assessment A21-93 [1] therefore excluded this outcome.

In its comments, the company has presented results on another operationalization of the composite renal morbidity outcome, comprising sustained eGFR reduction by ≥ 50%, end-stage renal disease (ESRD, defined as chronic dialysis or renal transplant or sustained eGFR < 15 mL/min/1.73 m^2), and renal death. However, the component of sustained eGFR reduction by ≥ 50% likewise suffers from uncertainty regarding its patient relevance and its severity being comparable to the remaining components. A total of 52% of EMPEROR-Reduced study participants exhibited an eGFR ≥ 60 mL/min/1.73m^2. Given this high baseline eGFR, a relative reduction in eGFR by ≥ 50% is not necessarily patient relevant and its consequence is therefore not comparable to the severity of the other components of the composite renal morbidity outcome (e.g. ESRD and renal death). Therefore, the operationalization of the composite renal morbidity outcome presented during the commenting procedure remains unsuitable for use in the benefit assessment of empagliflozin for chronic HF.

Results for the composite renal morbidity outcome comprising sustained eGFR reduction by ≥ 50%, ESRD and renal death are presented in Appendix A. The company submitted neither any effect estimators for the individual components of the composite outcome, nor Kaplan-Meier curves for the composite outcome or its individual components, nor exact results of a statistical test (p-values), nor subgroup analyses.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on added benefit of empagliflozin drawn in dossier assessment A21-93.

The following Table 1 shows the result of the benefit assessment of empagliflozin, taking into account dossier assessment A21-93 and the present addendum.

Table 1: Empagliflozin – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with symptomatic chronic heart failure with reduced ejection fraction[b]	Optimized standard therapy for the treatment of symptomatic chronic HF and underlying medical conditions, e.g. hypertension, cardiac arrhythmia, coronary heart disease, diabetes mellitus, hypercholesterolaemia and the concomitant symptoms	Hint of non-quantifiable added benefit

a. Presented is the ACT specified by the G-BA.
b. The conclusion on added benefit is based on the results of the EMPEROR-Reduced study. To qualify for inclusion in the EMPEROR-Reduced study, patients had to exhibit an LVEF ≤ 40% and meet additional inclusion criteria (including certain NT-proBNP thresholds). It remains unclear whether the observed effects can be extrapolated to other patients in the target population.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HF: heart failure; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-Brain Natriuretic Peptide

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Empagliflozin (Herzinsuffizienz) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 18.10.2021]. URL: https://www.iqwig.de/download/a21-93_empagliflozin_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Boehringer Ingelheim Pharma. Empagliflozin (Jardiance); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2021 [Accessed: 26.11.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/716/#dossier.

3. Boehringer Ingelheim Pharma. Stellungnahme zum IQWiG-Bericht Nr. 1217: Empagliflozin (Herzinsuffizienz) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/716/#beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A Results on the composite outcome regarding renal morbidity

Table 2: Results (morbidity) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study Outcome category Outcome	Empagliflozin + optimized standard therapy		Placebo + optimized standard therapy		Empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
EMPEROR-Reduced					
Morbidity					
Renal morbidity (composite outcome)[a]	1863	ND 18 (1.0)	1867	ND 33 (1.8)	0.52 [0.29; 0.92]; < 0.05
Sustained eGFR reduction by ≥ 50%:	1863	ND 18 (1.0[b])	1867	ND 22 (1.2[b])	ND
ESRD[c]	1863	ND 4 (0.2[b])	1867	ND 9 (0.5[b])	ND
Renal death	1863	ND 1 (0.1[b])	1867	ND 2 (0.1[b])	ND

a. The composite outcome comprises sustained eGFR reduction by ≥ 50%, ESRD and renal death.
b. IQWiG calculation.
c. ESRD comprises chronic dialysis or renal transplant or sustained eGFR < 15 mL/min/1.73 m².

CI: confidence interval; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; RCT: randomised controlled trial