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Dapagliflozin (type 2 diabetes mellitus) –

Addendum to Commission A19-53[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
RCT	randomized controlled trial
SAE	serious adverse event
SMQ	Standardized MedDRA Query

1 Background

On 12 November 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-53 (Dapagliflozin – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier for the benefit assessment of dapagliflozin in patients with type 2 diabetes mellitus [2], the pharmaceutical company (hereinafter referred to as "the company") performed an information retrieval for studies only for a subpopulation of the therapeutic indication (patients with increased cardiovascular risk). In this information retrieval, the company identified the DECLARE-TIMI 58 study, which it included in its benefit assessment. The company's dossier did not contain usable data for the overall rate of serious adverse events (SAEs).

With its comments [3], the company, on the one hand, subsequently submitted an information retrieval for studies in the total approval population of dapagliflozin in patients with type 2 diabetes mellitus. On the other, the company subsequently submitted analyses on overall rates of adverse events (AEs). The G-BA commissioned IQWiG to assess the literature search and these data subsequently submitted.

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 Information retrieval on the total approval population

For its dossier for the benefit assessment of dapagliflozin [2], the company only conducted an information retrieval on the research question defined by the company (patients with increased cardiovascular risk). The therapeutic indication of dapagliflozin also comprises patients without increased cardiovascular risk, however. Hence, the company had not comprehensively investigated the therapeutic indication of type 2 diabetes mellitus in its dossier. The company now subsequently submitted an information retrieval on the total approval population in its comments.

Research question

In the framework of its comments, the company divided the therapeutic indication into 6 research questions, 5 of which concurred with the specification of the G-BA (see Table 1). As in its dossier for the benefit assessment of dapagliflozin [2], the company additionally considered patients with increased cardiovascular risk separately.

Table 1: Research questions of the benefit assessment of dapagliflozin

Research question	Subindication[a]	ACT[b]
1	Monotherapy when diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance	▪ **Sulfonylurea** (glibenclamide or glimepiride)
2	Combination with one other blood-glucose lowering drug (except insulin, here metformin), when this, together with diet and exercise, does not provide adequate glycaemic control	▪ **Metformin + sulfonylurea** (glibenclamide or glimepiride) or ▪ metformin + empagliflozin or ▪ metformin + liraglutide[c]
3	Combination with one other blood-glucose lowering drug (except insulin and metformin), when this, together with diet and exercise, does not provide adequate glycaemic control	▪ **Metformin + sulfonylurea** (glibenclamide or glimepiride) or ▪ metformin + empagliflozin or ▪ metformin + liraglutide[c] or ▪ human insulin if metformin is not tolerated or contraindicated according to the SPC
4	Combination with at least 2 other blood-glucose lowering drugs (except insulin), when these, together with diet and exercise, do not provide adequate glycaemic control	▪ **Human insulin + metformin** or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ **human insulin** if, according to the SPC, the specified combination partners are not tolerated, contraindicated or not sufficiently effective due to advanced type 2 diabetes mellitus
5	Combination with insulin, without or with one other blood-glucose lowering drug, when this, together with diet and exercise, does not provide adequate glycaemic control	▪ **Optimization of the human insulin regimen (if applicable + metformin** or empagliflozin[c] or liraglutide[c])

a. Subdivisions of the therapeutic indication according to the G-BA.
b. Presentation of the respective 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. Empagliflozin or liraglutide, each in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for the operationalization, see inclusion criteria of the relevant studies for empagliflozin [4] and liraglutide [5]).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The information retrieval on the G-BA's 5 research questions is assessed below. The information retrieval on the research question additionally defined by the company is not assessed separately, as the patient population addressed in this research question is comprised by the G-BA's 5 research questions, which consider patients without or with increased cardiovascular risk.

Information retrieval of the company

The company's information regarding the information retrieval on the direct comparison based on randomized controlled trials (RCTs) can be found in Appendix 3 of its comments [3].

Inclusion criteria

For the systematic selection of studies, the company defined inclusion criteria that allow an adequate information retrieval for the 5 research questions defined by the G-BA. The inclusion criterion "comparator therapy" for each of the 5 research questions did not exactly concur with the G-BA's specification. However, in each case, the deviations resulted in an expansion, and not in a limitation compared with the G-BA's specification, so that no studies were excluded because of them.

Study list on dapagliflozin

In the framework of its comments, the company did not present a study list on the G-BA's 5 research questions. The company's study list in its dossier for the benefit assessment of dapagliflozin [2] was incomplete for the addendum, as it was limited to patients with increased cardiovascular risk.

Bibliographical literature search on dapagliflozin (last search on 8 October 2019)

For the comments, the company conducted the required literature search in bibliographical databases on the direct comparison based on RCTs. The company's search was suitable to guarantee the completeness of the search result for the bibliographical literature search.

Search in trial registries for studies on dapagliflozin (last search on 8 October 2019)

For the comments, the company conducted the required search in trial registries on the direct comparison based on RCTs. The company's search was suitable to guarantee the completeness of the search result for the search in trial registries.

Summary

The information retrieval conducted by the company on the direct comparison based on RCTs was unsuitable to guarantee the completeness of the search results, as the study list of the company was missing. However, it was already checked in the framework of the dossier assessment on dapagliflozin [1] whether there are RCTs of direct comparison for the research questions (last search on 16 July 2019), and no suitable study for the G-BA's 5 research questions was identified in the framework of this check. With the information retrieval subsequently submitted, the company also did not identify a relevant study on these research questions, nor did it identify any further studies on its additional research question.

2.2 Data subsequently submitted on side effects

In its dossier for the benefit assessment of dapagliflozin [2], the company had only presented analyses on the overall rate of SAEs (under the exclusion of late complications) that were observed until 30 days after treatment discontinuation. In case of treatment discontinuation, the DECLARE-TIMI 58 study recorded AEs until the last study visit. With its comments, the company now presented analyses that considered the total observation period.

In its dossier, the company had additionally presented an analysis of the overall rate of SAEs under exclusion of late complications, but had continued to record renal events and renal

complications. With its comments, the company now presented analyses for the overall rate of SAEs under exclusion of late complications including renal events and retinopathies. This analysis constitutes a sufficient approximation to the overall rate of SAEs under exclusion of late complications.

2.2.1 Results

Table 2 shows the results on overall rates of SAEs (under exclusion of late complications) under consideration of the data subsequently submitted by the company.

Table 2: Results (side effects) of the DECLARE-TIMI 58 study

Study Outcome category Outcome	Dapagliflozin		Placebo		Dapagliflozin vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
DECLARE-TIMI 58					
Side effects					
SAEs (nonfatal, under exclusion of late complications)[b, c]	8574	2496 (29.1)	8569	2737 (31.9)	0.91 [0.87; 0.95]; < 0.001

a. p-value from Wald test.
b. Follow-up observation until the last visit.
c. Under exclusion of the following late complications: death (including cardiovascular death), myocardial infarction, ischaemic stroke, hospitalization due to cardiac failure, unstable angina pectoris, revascularization, renal events and retinopathies.

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; RR: relative risk; SAE: serious adverse event

2.2.2 Summary

Under consideration of dossier assessment A19-53 [1] and the present addendum, there are both advantages and disadvantages of dapagliflozin + standard therapy in comparison with placebo + standard therapy. Changes resulting from the data subsequently submitted by the company in the commenting procedure are presented in *italics* below. There are statistically significant results in favour of dapagliflozin + standard therapy in comparison with placebo + standard therapy for the following outcomes:

- cardiac failure:
  - hospitalization due to cardiac failure
  - severe cardiac failure (Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ] cardiac failure)
- renal disorder
- *SAEs (nonfatal, under exclusion of late complications)*
- bladder carcinoma

There are statistically significant results to the disadvantage of dapagliflozin + standard therapy in comparison with placebo + standard therapy for the following outcomes:

- discontinuation due to AEs
  - discontinuation due to urinary tract infection (AEs)
  - discontinuation due to genital infection (AEs)
- definite diabetic ketoacidosis (AEs)

No statistically significant differences between the treatment groups were shown for the other outcomes presented, or no usable data were available.

3 References

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