IQWiG Reports – Commission No. A19-93

# Dapagliflozin/metformin (type 2 diabetes mellitus) –

## Addendum to Commission A19-52[1]

## Addendum

Commission: A19-93
Version: 1.0
Status: 29 November 2019

[1] Translation of addendum A19-93 *Dapagliflozin/Metformin (Diabetes mellitus Typ 2)* – Addendum zum Auftrag A19-52 (Version 1.0; Status: 29 November 2019). 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**
Dapagliflozin/metformin (type 2 diabetes mellitus) – Addendum to Commission A19-52

**Commissioning agency**
Federal Joint Committee

**Commission awarded on**
12 November 2019

**Internal Commission No.**
A19-93

**Address of publisher**
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**Keywords:** Dapagliflozin, Metformin, Diabetes Mellitus – Type 2, Benefit Assessment, NCT01730534

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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 |
| PT | Preferred Term |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SMQ | Standardized MedDRA Query |
| SOC | System Organ Class |

# 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 A19-52 (Dapagliflozin/metformin – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier for the benefit assessment of dapagliflozin/metformin 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 presented a subpopulation of the DECLARE-TIMI 58 study for the assessment of the fixed combination of dapagliflozin and metformin: patients who had received at least 1700 mg of metformin at baseline. However, the company's dossier contained no data or no usable data for several outcomes for this subpopulation.

With its comments [3], the company, on the one hand, subsequently submitted an information retrieval for studies in the total approval population of dapagliflozin/metformin in patients with type 2 diabetes mellitus. On the other, the company subsequently submitted analyses on adverse events (AEs) – overall rates and specific AEs – for the subpopulation of the DECLARE-TIMI 58 study. 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/metformin [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/metformin 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 4 research questions, 3 of which concurred with the specification of the G-BA (see Table 1). As in its dossier for the benefit assessment of dapagliflozin/metformin [2], the company additionally considered patients with increased cardiovascular risk separately.

Table 1: Research questions of the benefit assessment of dapagliflozin/metformin

| Research question | Subindication[a] | ACT[b] |
|---|---|---|
| 1 | 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<br>▪ metformin + empagliflozin or<br>▪ metformin + liraglutide[c] |
| 2 | Combination with at least 2 other blood-glucose lowering drugs (including metformin, except insulin), when these, together with diet and exercise, do not provide adequate glycaemic control | ▪ **Human insulin + metformin** or<br>▪ human insulin + empagliflozin[c] or<br>▪ human insulin + liraglutide[c] or<br>▪ **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 |
| 3 | Combination with insulin (with one other blood-glucose lowering drug, here metformin), 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

The information retrieval on the G-BA's 3 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 3 research questions, which consider patients without and 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 3 research questions defined by the G-BA. The inclusion criterion "comparator therapy" for each of the 3 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. The same applied to the inclusion criterion "intervention", for which the company only cited "dapagliflozin" and not "dapagliflozin/metformin".

***Study list on dapagliflozin/metformin***

In the framework of its comments, the company did not present a study list on the G-BA's 3 research questions. The company's study list in its dossier for the benefit assessment of dapagliflozin/metformin [2] was incomplete for the addendum, as it was limited to patients with increased cardiovascular risk.

***Bibliographical literature search on dapagliflozin/metformin (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/metformin (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/metformin [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

3 research questions was identified in the framework of this check. With the information retrieval subsequently submitted, the company also did not identify any relevant studies 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/metformin [2], the company had only presented analyses on serious adverse events (SAEs) that were observed until 30 days after treatment discontinuation. For non-serious and specific AEs (with the exception of malignancies), the company had only presented analyses that considered events occurring until 7 days after treatment discontinuation. In case of treatment discontinuation, the DECLARE-TIMI 58 study recorded AEs until the last study visit, however. 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 side effects (overall rates and specific AEs) under consideration of the data subsequently submitted by the company. The results on common SAEs and discontinuations due to AEs can be found in Appendix A.

Table 2: Results (side effects) of the DECLARE-TIMI 58 study (subpopulation, at least 1700 mg metformin at baseline)

| Study<br>Outcome category<br>Outcome | Dapagliflozin + metformin<br>N | <br>Patients with event n (%) | Placebo + metformin<br>N | <br>Patients with event n (%) | Dapagliflozin + metformin vs. placebo + metformin<br>RR [95% CI]; p-value[a] |
|---|---|---|---|---|---|
| **DECLARE-TIMI 58** | | | | | |
| **Side effects[b]** | | | | | |
| AEs (supplementary information) | No usable data[c] | | | | |
| SAEs (nonfatal, under exclusion of late complications)[d] | 4622 | 1263 (27.3) | 4689 | 1455 (31.0) | 0.88 [0.83; 0.94]; < 0.001 |
| Discontinuation due to AEs | 4622 | 310 (6.7) | 4689 | 301 (6.4) | 1.04 [0.90; 1.22]; 0.575 |
| Hypoglycaemia (PT, SAEs) | 4622 | 32 (0.7) | 4689 | 48 (1.0) | 0.68 [0.43; 1.06]; 0.084[e] |
| Discontinuation due to urinary tract infection[f, g] (AEs) | 4622 | 27 (0.6) | 4689 | 20 (0.4) | 1.37 [0.77; 2.44]; 0.285 |
| Discontinuation due to genital infection[f, g] (AEs) | 4622 | 36 (0.8) | 4689 | 3 (0.1) | 12.17 [3.75; 39.50]; < 0.001 |
| DKAs[f, h] (all, AEs) | No analyses available | | | | |
| Definite DKAs | 4622 | 12 (0.3[i]) | 4689 | 6 (0.1[i]) | 2.03 [0.76; 5.40]; 0.153[e] |
| Probable DKAs | 4622 | 3 (0.1[i]) | 4689 | 3 (0.1[i]) | 1.01 [0.20; 5.02]; > 0.999[e] |
| Possible DKAs | No analyses available | | | | |
| Symptoms of volume depletion[f] (AEs) | 4622 | 125 (2.7) | 4689 | 107 (2.3) | 1.19 [0.92; 1.53]; 0.192 |
| Respiratory, thoracic and mediastinal disorders (System Organ Class [SOC], SAEs) | 4622 | 97 (2.1) | 4689 | 134 (2.9) | 0.73 [0.57; 0.95]; 0.019[e] |
| Hepatobiliary disorders (SOC, SAEs) | 4622 | 52 (1.1) | 4689 | 77 (1.6) | 0.69 [0.48; 0.97]; 0.033[e] |

a. p-value from Wald test.
b. Follow-up observation until the last visit.
c. Not all AEs were completely documented in the study (only SAEs, discontinuations due to AEs, and predefined AEs of special interest).
d. 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.
e. Institute's calculation, unconditional exact test, CSZ method according to [6].
f. Recorded using a predefined PT collection of the company.
g. As the total proportion of AEs was not recorded by the company, the discontinuations due to this AE were used for this AE.
h. Adjudicated by an outcome committee.
i. Institute's calculation.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; DKA: diabetic ketoacidosis; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

### 2.2.2 Summary

Under consideration of dossier assessment A19-52 [1] and the present addendum, there are mostly advantages of dapagliflozin/metformin + 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/metformin + 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
- bladder carcinoma
- *SAEs (nonfatal, under exclusion of late complications)*
- *respiratory, thoracic and mediastinal disorders*
- *hepatobiliary disorders*

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

- *discontinuation due to genital infection*

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

## 3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dapagliflozin/Metformin (Diabetes mellitus Typ 2): Nutzenbewertung gemäß § 35a SGB V (neue wissenschaftliche Erkenntnisse); Dossierbewertung; Auftrag A19-52 [online]. 27.09.2019 [Accessed: 08.10.2019]. (IQWiG-Berichte; Volume 819). URL: https://www.iqwig.de/download/A19-52_Dapagliflozin-Metformin_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. AstraZeneca. Dapagliflozin/Metformin (Xigduo 5 mg/850 mg Filmtabletten) (Xigduo 5 mg/1.000 mg Filmtabletten): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 18.06.2019 [Accessed: 09.10.2019]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/470/.

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4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373(22): 2117-2128.

5. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375(4): 311-322.

6. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

## Appendix A – Results on the most common side effects

The following tables present the MedDRA SOCs and Preferred Terms (PTs) for the overall rates of SAEs on the basis of the following criteria:

- overall rates of SAEs: events that occurred in at least 5% of the patients in one study arm
- in addition for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in one study arm

For the outcome "discontinuation due to AEs", all events (SOCs/PTs) that resulted in discontinuation in at least 10 patients in one study arm are presented.

No usable data were available for the overall rate of AEs, as the company did not conduct a complete documentation of all AEs (only SAEs, discontinuations due to AEs, and predefined AEs of special interest). Hence, the events for the overall rates of AEs at SOC and PT level are not presented in the following tables.

Table 3: Common SAEs[a] in the DECLARE-TIMI 58 study (subpopulation, at least 1700 mg metformin at baseline)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Dapagliflozin + metformin N = 4622** | **Placebo + metformin N = 4689** |
| **DECLARE-TIMI 58** | | |
| **Overall rate of SAEs** | 1643 (35.5) | 1818 (38.8) |
| Cardiac disorders | 628 (13.6) | 668 (14.2) |
| Angina unstable | 135 (2.9) | 141 (3.0) |
| Acute myocardial infarction | 139 (3.0) | 132 (2.8) |
| Cardiac failure | 79 (1.7) | 114 (2.4) |
| Angina pectoris | 87 (1.9) | 82 (1.7) |
| Atrial fibrillation | 60 (1.3) | 74 (1.6) |
| Myocardial infarction | 57 (1.2) | 62 (1.3) |
| Coronary artery disease | 59 (1.3) | 43 (0.9) |
| Cardiac failure congestive | 40 (0.9) | 59 (1.3) |
| Infections and infestations | 340 (7.4) | 422 (9.0) |
| Pneumonia | 95 (2.1) | 104 (2.2) |
| Cellulitis | 44 (1.0) | 53 (1.1) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 283 (6.1) | 293 (6.2) |
| Nervous system disorders | 252 (5.5) | 252 (5.4) |
| Cerebrovascular accident | 59 (1.3) | 49 (1.0) |
| Ischaemic stroke | 54 (1.2) | 38 (0.8) |
| Injury, poisoning and procedural complications | 172 (3.7) | 175 (3.7) |
| Vascular disorders | 156 (3.4) | 161 (3.4) |
| General disorders and administration site conditions | 138 (3.0) | 167 (3.6) |
| Non-cardiac chest pain | 48 (1.0) | 60 (1.3) |
| Musculoskeletal and connective tissue disorders | 135 (2.9) | 157 (3.3) |
| Osteoarthritis | 51 (1.1) | 47 (1.0) |
| Gastrointestinal disorders | 136 (2.9) | 147 (3.1) |
| Metabolism and nutrition disorders | 113 (2.4) | 157 (3.3) |
| Hypoglycaemia | 32 (0.7) | 48 (1.0) |
| Renal and urinary disorders | 86 (1.9) | 164 (3.5) |
| Acute kidney injury | 42 (0.9) | 77 (1.6) |
| Respiratory, thoracic and mediastinal disorders | 97 (2.1) | 134 (2.9) |
| Hepatobiliary disorders | 52 (1.1) | 77 (1.6) |
| Skin and subcutaneous tissue disorders | 47 (1.0) | 45 (1.0) |

a. Information refers to SAEs without exclusion of late complications.
b. MedDRA version 21.0.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class

Table 4: Common discontinuations due to AEs in the DECLARE-TIMI 58 study (subpopulation, at least 1700 mg metformin at baseline)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[a] PT[a]** | **Dapagliflozin + metformin N = 4622** | **Placebo + metformin N = 4689** |
| **DECLARE-TIMI 58** | | |
| **Overall rate of discontinuations due to AEs** | 310 (6.7) | 301 (6.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 52 (1.1) | 65 (1.4) |
| Bladder cancer | 2 (0) | 12 (0.3) |
| Infections and infestations | 68 (1.5) | 36 (0.8) |
| Urinary tract infection | 16 (0.3) | 12 (0.3) |
| Renal and urinary disorders | 48 (1.0) | 50 (1.1) |
| Acute kidney injury | 5 (0.1) | 14 (0.3) |
| Renal impairment | 10 (0.2) | 8 (0.2) |
| Nervous system disorders | 20 (0.4) | 25 (0.5) |
| Metabolism and nutrition disorders | 12 (0.3) | 26 (0.6) |
| Reproductive system and breast disorders | 33 (0.7) | 5 (0.1) |
| Balanoposthitis | 11 (0.2) | 1 (0) |
| Cardiac disorders | 18 (0.4) | 18 (0.4) |
| Gastrointestinal disorders | 12 (0.3) | 21 (0.4) |
| Investigations | 14 (0.3) | 12 (0.3) |
| Skin and subcutaneous tissue disorders | 6 (0.1) | 11 (0.2) |

a. MedDRA version 21.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; SOC: System Organ Class