

IQWiG Reports – Commission No. A12-18

Dapagliflozin – Benefit assessment according to § 35a Social Code Book V¹

Extract

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Table of contents

| | |
|---|-----------|
| List of tables..... | iv |
| List of abbreviations..... | v |
| 2 Benefit assessment | 1 |
| 2.1 Executive summary of the benefit assessment..... | 1 |
| 2.2 Research question | 7 |
| 2.3 Information retrieval and study pool..... | 10 |
| 2.3.1 Studies included | 11 |
| 2.3.1.1 Dapagliflozin monotherapy (coding A)..... | 11 |
| 2.3.1.2 Combination therapy of dapagliflozin and metformin (coding B) | 12 |
| 2.3.1.3 Combination therapy of dapagliflozin and sulfonylureas (coding C) | 13 |
| 2.3.1.4 Combination therapy of dapagliflozin and insulin (coding D)..... | 13 |
| 2.3.1.5 Summary..... | 14 |
| 2.4 Results on added benefit..... | 15 |
| 2.5 Extent and probability of added benefit | 15 |
| 2.5.1 Dapagliflozin monotherapy (coding A) | 15 |
| 2.5.2 Combination therapy of dapagliflozin and metformin (coding B)..... | 15 |
| 2.5.3 Combination therapy of dapagliflozin and sulfonylureas (coding C) | 15 |
| 2.5.4 Combination therapy of dapagliflozin and insulin (coding D)..... | 16 |
| 2.6 List of included studies | 16 |
| References for English extract | 16 |

List of tables³

Table 2: Overview of the ACT for dapagliflozin..... 2

Table 3: Overview of the ACT for dapagliflozin..... 7

³ Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

| Abbreviation | Meaning |
|---------------------|--|
| ACT | appropriate comparator therapy |
| DPP-4 | dipeptidyl peptidase 4 |
| eGFR | estimated glomerular filtration rate |
| G-BA | <i>Gemeinsamer Bundesausschuss</i> (Federal Joint Committee) |
| GLP-1 | glucagon-like peptide 1 |
| IQWiG | <i>Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen</i> (Institute for Quality and Efficiency in Health Care) |
| RCT | randomized controlled trial |
| SGB | <i>Sozialgesetzbuch</i> (Social Code Book) |
| SPC | Summary of Product Characteristics |

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dapagliflozin. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to “the company”). The dossier was sent to IQWiG on 14.12.2012.

Research question

The benefit assessment of dapagliflozin was conducted according to the approval status for the following therapeutic indication: treatment of adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control.

Dapagliflozin is approved in monotherapy and in add-on combination therapy.

- **Monotherapy:** when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered unsuitable due to intolerance.
- **Add-on combination therapy:** in combination with other glucose-lowering drugs including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

According to the information provided in the Summary of Product Characteristics (SPC), use of dapagliflozin is not recommended for the following patient groups. These groups are therefore not considered in this benefit assessment:

- Patients with moderate to severe renal impairment (creatinine clearance < 60 mL/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m²), or
- Patients who are 75 years or older at the start of dapagliflozin treatment, or
- Patients receiving loop diuretics.

According to the company's consultation request to the G-BA, an appropriate comparator therapy (ACT) was specified for each of 4 approved subindications.

Table 2: Overview of the ACT for dapagliflozin

| Coding in the company's dossier | Subindication | ACT specified by the G-BA |
|---|--|---|
| A | Dapagliflozin monotherapy | Sulfonylureas (glibenclamide or glimepiride) |
| B | Combination therapy of dapagliflozin and metformin | Sulfonylureas (glibenclamide or glimepiride) and metformin |
| C | Combination therapy of dapagliflozin and sulfonylureas | Metformin and sulfonylureas (glibenclamide or glimepiride) |
| D | Combination therapy of dapagliflozin and insulin <ul style="list-style-type: none"> ▪ dapagliflozin + insulin + 1 to 2 OAD (subpopulation D1^a) ▪ dapagliflozin + insulin alone (subpopulation D2^a) | For both subpopulations: metformin + human insulin, or human insulin alone for patients in whom metformin is not sufficiently effective or is not tolerated |
| a: designation in the company's dossier ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic | | |

Dapagliflozin monotherapy

The benefit assessment of dapagliflozin in monotherapy was conducted according to the SPC for patients for whom use of metformin is considered unsuitable due to intolerance. This deviated from the company's approach, which did not define metformin intolerance as a criterion for study inclusion.

Therapy with sulfonylureas (glibenclamide or glimepiride) specified by the G-BA was used as ACT for this benefit assessment. This deviated from the company's approach, which cited sulfonylureas without limitation to the drugs specified by the G-BA, as ACT.

Moreover, the company defined an additional patient group in whom, from the point of view of the company, sulfonylureas cannot be used, and in whom insulin is not yet indicated. It cited dipeptidyl peptidase 4 (DPP-4) inhibitors as alternative comparator therapy for these patients. It did not provide clear characteristics of this patient population. The patient population cited by the company was therefore seen as a not clearly definable subpopulation in the subindication and not considered in this benefit assessment.

Combination therapy of dapagliflozin and metformin

The benefit assessment of dapagliflozin in combination therapy with metformin was conducted according to the SPC for patients in whom metformin (together with diet and exercise) does not provide adequate glycaemic control. Therapy with sulfonylureas (glibenclamide or glimepiride) + metformin specified by the G-BA was used as ACT. This deviated from the company's approach, which cited sulfonylureas + metformin without limitation to the drugs glibenclamide and glimepiride specified by the G-BA, as ACT for this indication. The company advised that the added benefit should be derived on the basis of an

approval study in which the sulfonylurea glipizide had been used. However, as the company itself pointed out in its dossier, glipizide has no longer been approved in Germany since 2007, and is therefore unsuitable as ACT. The company justified the admissibility of a comparison with glipizide instead of glibenclamide or glimepiride mainly with the comparability of glipizide with these drugs. The data presented by the company were insufficient to support this assumption, however. You can find more details on this in the benefit assessment of the fixed combination of saxagliptin and metformin (Saxagliptin/metformin – Benefit assessment according to § 35a SGB V). In the corresponding dossier, the same company provided an identical rationale.

Moreover, the company defined an additional patient group in whom sulfonylureas are unsuitable, and in whom insulin is not yet indicated. The company did not provide further characteristics of this patient population. The patient population cited by the company was therefore seen as a not clearly definable subpopulation in the subindication and not considered in this benefit assessment.

Combination therapy of dapagliflozin and sulfonylureas

The benefit assessment of dapagliflozin in combination therapy with sulfonylureas was conducted according to the SPC for patients in whom sulfonylureas (together with diet and exercise) do not provide adequate glycaemic control. Therapy with metformin + sulfonylureas (glibenclamide or glimepiride) specified by the G-BA was used as ACT. This deviated from the company's approach, which cited metformin + sulfonylureas without limitation to the drugs glibenclamide and glimepiride as ACT for this indication.

Furthermore, the patient population for whom metformin is unsuitable as component of the ACT was also considered. For this population, treatment with human insulin (if applicable, in combination with sulfonylureas) resulting from the G-BA's consultation documents is considered to be the ACT. The company did not investigate this research question in the dossier, however.

Instead, the company limited the patient population with metformin intolerance to those for whom insulin is not yet an option, and cited the combination of sulfonylurea and a DPP-4 inhibitor as alternative comparator treatment. The limitation of the patient population with metformin intolerance to those for whom insulin is not yet an option was not accepted. It was unclear what the characteristics of this population are and how they differ from those for whom insulin is indicated. The patient population cited by the company was therefore seen as a not clearly definable subpopulation in the subindication and not considered in this benefit assessment.

Combination therapy of dapagliflozin and insulin

The benefit assessment of dapagliflozin in combination with insulin was conducted according to the SPC for patients in whom insulin (together with diet and exercise) does not provide adequate glycaemic control. The comparator therapy specified by the G-BA was used as ACT

(metformin + human insulin, or human insulin alone for patients for whom metformin is not an option or ineffective). The company primarily stated to follow the ACT specified by the G-BA, but the dossier contained contradictory information on the implementation of the ACT (e.g. use of insulin instead of human insulin, expansion of the ACT with other oral antidiabetics).

Additional comment

The subindications considered by the company (codings A to D) did not cover the entire therapeutic indication of dapagliflozin. Combinations with other oral antidiabetics such as DPP-4 inhibitors or glucagon-like peptide 1 (GLP-1) analogues are also approved besides the subindications cited by the company. Furthermore, the approval status does not exclude the use of dapagliflozin in oral triple combination. The company did not provide any data on this, however; hence an added benefit cannot be derived.

Results

Dapagliflozin monotherapy

The company did not present any direct comparative study on dapagliflozin monotherapy versus the ACT (sulfonylureas [glibenclamide or glimepiride]).

The company conducted an adjusted indirect comparison of dapagliflozin versus sulfonylureas (without limitation to the drugs glibenclamide and glimepiride). The company chose placebo or diet as intermediate comparator. On the dapagliflozin side, the company included the placebo-controlled study MB102013. According to the inclusion criteria of this study it could be assumed that the majority of patients enrolled did not have metformin intolerance and therefore did not receive approval-compliant treatment. The same was true for the 5 studies on the sulfonylurea side identified by the company. Hence the studies presented for the indirect comparison were unsuitable for drawing conclusions on the added benefit of dapagliflozin in monotherapy versus the ACT, and were not included in this benefit assessment.

Combination therapy of dapagliflozin and metformin

The company did not present any direct comparative studies on the combination therapy of dapagliflozin and metformin versus the ACT (sulfonylurea [glibenclamide or glimepiride] + metformin). The only study the company included in the assessment, study D1690C00004, conducted a comparison of the combination of metformin and dapagliflozin versus metformin and glipizide. For the reasons stated above, this study was unsuitable for a direct comparison versus the ACT.

Combination therapy of dapagliflozin and sulfonylureas

The company did not present any direct comparative studies on the combination therapy of dapagliflozin and sulfonylureas versus the ACT (sulfonylureas [glibenclamide or glimepiride] + metformin).

The company conducted an adjusted indirect comparison of dapagliflozin + sulfonylureas versus metformin + sulfonylureas (without limitation to the drugs glibenclamide and glimepiride). The company chose sulfonylureas + placebo as intermediate comparator. On the dapagliflozin side, the company included the study D1690C00005, which compared treatment with glimepiride + dapagliflozin with administration of glimepiride + placebo. The 2 studies identified by the company on the comparator side (DeFronzo 1995 and Goldstein 2003) were not relevant for the research question, however. According to the specifications in the study protocol, all patients in the study of DeFronzo 1995 received a glibenclamide dose of 20 mg/day (equivalent to 15 mg/day of the micronized form used in Germany). A change of this dosage during the course of the study was not envisaged. This dose considerably exceeds the maximal dose of 10.5 mg/day approved in Germany. In the study Goldstein 2003, the sulfonylurea glipizide, which is not approved in Germany, was used. In addition, the study duration (18 weeks) did not meet the inclusion criterion of a minimal study duration of 24 weeks. Hence an indirect comparison versus the ACT cannot be conducted based on the available data.

Combination therapy of dapagliflozin and insulin

The company presented 3 randomized placebo-controlled trials on the subindication "dapagliflozin in combination with insulin" (D1690C00006, D1690C00018 and D1690C00019), to derive an added benefit.

All 3 studies were unsuitable for assessing the added benefit because, in the comparator groups, it was largely prohibited to adapt the insulin therapy to individual requirements. Patients who received insulin and up to 2 additional oral antidiabetics and did not achieve sufficient glycaemic control under this therapy were enrolled in the placebo-controlled study D1690C00006. D1690C00018 and D1690C00019 were placebo-controlled studies with patients who did not achieve sufficient glycaemic control under prior antidiabetic treatment (with and without insulin). Patients in both treatment arms in all 3 studies were required to continue their prior treatment with insulin (with or without oral antidiabetic) unchanged, i.e. it was neither allowed to change the type of insulin nor the type of insulin therapy. Only in the study D1690C00006, it became possible to change regimen almost 1 year after enrolment of the first patient by amendment to the study protocol. However, this was only possible for the second half of the study (from week 25), and only if unexpected hypoglycaemia occurred with high levels of fasting plasma glucose or HbA1c at the same time. The insulin dose could only be increased as an emergency medication in very high levels of fasting plasma glucose or HbA1c, and reduced in an increased risk of hypoglycaemia. Antidiabetic therapy would usually already be optimized in less pronounced fluctuations of blood glucose levels so that hypoglycaemia and hyperglycaemia do not occur in the first place, and not as a reaction to these events.

Because of the lack of opportunities for optimization – particularly in the respective comparator groups – the 3 studies mentioned were unsuitable for drawing conclusions on the added benefit of dapagliflozin in combination with insulin versus the ACT (metformin +

human insulin, or human insulin alone for patients for whom metformin is not an option or ineffective).

Moreover, the company used the data of the placebo-controlled studies to form different subpopulations from the study arms, which broke randomization. These analyses were unsuitable for proving an added benefit from a methodological point of view already.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

On the basis of the results presented, the extent and probability of the added benefit of dapagliflozin in the 4 subindications investigated by the company is assessed as follows:

Dapagliflozin monotherapy

There is no proof of an added benefit of dapagliflozin monotherapy in comparison with the ACT specified by the G-BA. Hence there are no patient groups, for whom a therapeutically important added benefit could be derived.

Combination therapy of dapagliflozin and metformin

There is no proof of an added benefit of the combination therapy of dapagliflozin and metformin in comparison with the ACT specified by the G-BA. Hence there are no patient groups, for whom a therapeutically important added benefit could be derived.

Combination therapy of dapagliflozin and sulfonylureas

There is no proof of an added benefit of the combination therapy of dapagliflozin and sulfonylureas in comparison with the ACT specified by the G-BA. Hence there are no patient groups, for whom a therapeutically important added benefit could be derived.

Combination therapy of dapagliflozin and insulin

There is no proof of an added benefit of the combination therapy of dapagliflozin and insulin (with up to 2 additional oral antidiabetics) in comparison with the ACT specified by the G-BA. Hence there are no patient groups, for whom a therapeutically important added benefit could be derived.

The decision on added benefit is made by the G-BA.

⁴ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research question

The benefit assessment of dapagliflozin was conducted according to the approval status [3] for the following therapeutic indication: treatment of adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control.

Dapagliflozin is approved in monotherapy and in add-on combination therapy.

- **Monotherapy:** when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered unsuitable due to intolerance.
- **Add-on combination therapy:** in combination with other glucose-lowering drugs including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

According to the information provided in the SPC, use of dapagliflozin is not recommended for the following patient groups. These groups are therefore not considered in this benefit assessment:

- Patients with moderate to severe renal impairment (creatinine clearance < 60 mL/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m²), or
- Patients who are 75 years or older at the start of dapagliflozin treatment, or
- Patients receiving loop diuretics.

According to the company's consultation request to the G-BA, an ACT was specified for each of the 4 approved subindications.

Table 3: Overview of the ACT for dapagliflozin

| Coding in the company's dossier | Subindication | ACT specified by the G-BA |
|---|--|---|
| A | Dapagliflozin monotherapy | Sulfonylureas (glibenclamide or glimepiride) |
| B | Combination therapy of dapagliflozin and metformin | Sulfonylureas (glibenclamide or glimepiride) and metformin |
| C | Combination therapy of dapagliflozin and sulfonylureas | Metformin and sulfonylureas (glibenclamide or glimepiride) |
| D | Combination therapy of dapagliflozin and insulin <ul style="list-style-type: none"> ▪ dapagliflozin + insulin + 1 to 2 OAD (subpopulation D1^a) ▪ dapagliflozin + insulin alone (subpopulation D2^a) | For both subpopulations: metformin + human insulin, or human insulin alone for patients in whom metformin is not sufficiently effective or is not tolerated |
| a: designation in the company's dossier ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic | | |

Dapagliflozin monotherapy (coding A)

The benefit assessment of dapagliflozin in monotherapy was conducted according to the SPC [3] for patients for whom use of metformin is considered unsuitable due to intolerance. This deviated from the company's approach, which did not define metformin intolerance as a criterion for study inclusion. From the point of view of the company, there is no difference in the efficacy of dapagliflozin between patients who have metformin intolerance and patients for whom metformin is indicated. The company did not provide proof of the transferability of the results. The company's rationale is not accepted in the benefit assessment (see Section 2.7.2.1.1 of the full dossier assessment).

Moreover, the company defined an additional patient group in whom, from the point of view of the company, sulfonylureas cannot be used, and in whom insulin is not yet indicated. It cited DPP-4 inhibitors as alternative comparator therapy for these patients. It did not provide characteristics of this patient population. The patient population cited by the company was seen as a not clearly definable subpopulation in the subindication and therefore not considered in this benefit assessment (see Section 2.7.1.1 of the full dossier assessment).

Therapy with sulfonylureas (glibenclamide or glimepiride) specified by the G-BA was used as ACT for this benefit assessment. This deviated from the company's approach, which cited sulfonylureas without limitation to the drugs specified by the G-BA, as ACT (see Section 2.7.1.1 of the full dossier assessment).

Combination therapy of dapagliflozin and metformin (coding B)

The benefit assessment of dapagliflozin in combination therapy with metformin was conducted according to the SPC [3] for patients in whom metformin (together with diet and exercise) does not provide adequate glycaemic control. This deviated from the company's approach, which defined a patient group for this indication, for which sulfonylureas are not an option and for whom insulin is not yet indicated. The company did not provide further characteristics of this patient population. The patient population cited by the company was therefore seen as a not clearly definable subpopulation in the subindication and not considered in this benefit assessment (see Section 2.7.1.2 of the full dossier assessment).

Therapy with sulfonylureas (glibenclamide or glimepiride) + metformin specified by the G-BA was used as ACT for this benefit assessment. This deviated from the company's approach, which cited sulfonylureas + metformin without limitation to the drugs glibenclamide and glimepiride specified by the G-BA, as ACT for this indication. The company advised that the added benefit should be derived on the basis of an approval study in which the sulfonylurea glipizide had been used. However, as the company itself pointed out in its dossier, glipizide has no longer been approved in Germany since 2007, and is therefore unsuitable as ACT. The company justified the admissibility of a comparison with glipizide instead of glibenclamide or glimepiride mainly with the comparability of glipizide with these drugs. The data presented by the company were insufficient to support this assumption, however. You can find more information on this in the benefit assessment of the fixed

combination of saxagliptin and metformin [4]. In the corresponding dossier, the same company provided an identical rationale.

Combination therapy of dapagliflozin and sulfonylureas (coding C)

The benefit assessment of dapagliflozin in combination therapy with sulfonylureas was conducted according to the SPC [3] for patients in whom sulfonylureas (together with diet and exercise) do not provide adequate glycaemic control. Furthermore, the patient population for whom metformin is unsuitable as component of the ACT was also considered. This was justified by the fact that sulfonylureas in monotherapy are mainly an option as second-choice drugs [5,6] in case of metformin intolerance or a contraindication to metformin. It can therefore be assumed that, if monotherapy with sulfonylureas was done, this was often the case because of metformin intolerance. Metformin cannot be used as combination partner in these patients.

Instead, the company limited the patient population with metformin intolerance to those for whom insulin is not yet an option, and cited the combination of sulfonylurea and a DPP-4 inhibitor as alternative comparator treatment. The limitation of the patient population with metformin intolerance to those for whom insulin is not yet an option was not accepted. It was unclear what the characteristics of this population are and how they differ from those for whom insulin is indicated. The patient population cited by the company was seen as a not clearly definable subpopulation in the subindication and therefore not considered in this benefit assessment (see Section 2.7.1.3 of the full dossier assessment).

Therapy with metformin + sulfonylureas (glibenclamide, glimepiride) specified by the G-BA was used as ACT for this benefit assessment. This deviated from the company's approach, which cited metformin + sulfonylureas without limitation to the drugs glibenclamide and glimepiride as ACT for this indication. For the population with metformin intolerance considered in the benefit assessment, treatment with human insulin (if applicable, in combination with sulfonylureas) resulting from the G-BA's consultation documents is considered to be the ACT. The company did not investigate this research question in the dossier, however.

Combination therapy of dapagliflozin and insulin (coding D)

The benefit assessment of dapagliflozin in combination with insulin was conducted according to the SPC [3] for patients in whom insulin (together with diet and exercise) does not provide adequate glycaemic control. Furthermore, the patient population for whom metformin is unsuitable was also considered. In particular, the following 2 treatment situations were taken into account:

- Combination of dapagliflozin and insulin and 1 or 2 additional oral antidiabetics
- Combination of dapagliflozin and insulin alone

The comparator therapy specified by the G-BA (metformin + human insulin, or human insulin alone for patients for whom metformin is not an option or ineffective) was used as ACT in this benefit assessment. The company primarily stated to follow the ACT specified by the G-BA, but the dossier contained contradictory information on the implementation of the ACT (e.g. use of insulin instead of human insulin, expansion of the ACT with other oral antidiabetics).

Summary

In summary, the assessment of dapagliflozin in each of the 4 subindications investigated by the company was conducted versus the ACTs specified by the G-BA, as detailed below:

- Dapagliflozin monotherapy: sulfonylureas (glibenclamide or glimepiride)
- Combination therapy of dapagliflozin and metformin: sulfonylureas (glibenclamide or glimepiride) and metformin
- Combination therapy of dapagliflozin and sulfonylureas: metformin and sulfonylureas (glibenclamide or glimepiride)
- Combination therapy of dapagliflozin and insulin (without or with up to 2 additional oral antidiabetics): metformin + human insulin, or human insulin alone for patients in whom metformin is not sufficiently effective or is not tolerated.

The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs). Only studies of a minimal duration of 24 weeks were included.

Additional comment

The subindications considered by the company (codings A to D) did not cover the entire therapeutic indication of dapagliflozin. Combinations with other oral antidiabetics such as DPP-4 inhibitors or GLP-1 analogues are also approved besides the subindications cited by the company. Furthermore, the approval status does not exclude the use of dapagliflozin in oral triple combination. The company did not provide any data on this, however, hence an added benefit cannot be derived.

Further information about the research question can be found in Modules 3A-D, Sections 3.1, and Modules 4A-D, Sections 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Dapagliflozin monotherapy (coding A)

Sources of the company in the dossier:

- Study list on dapagliflozin (studies completed up to 29.10.2012)
- Search in trial registries for studies on dapagliflozin (last search 29.10.2012)

- Bibliographical literature search and search in trial registries for studies on the ACT sulfonylurea (last search in bibliographical databases 22.10.2012, and in trial registries 26.10.2012)

Combination therapy of dapagliflozin and metformin (coding B)

Sources of the company in the dossier:

- Study list on dapagliflozin in combination with metformin (studies completed up to 29.10.2012)
- Search in trial registries for studies on dapagliflozin (last search 29.10.2012)

Combination therapy of dapagliflozin and sulfonylureas (coding C)

Sources of the company in the dossier:

- Study list on dapagliflozin in combination with sulfonylureas (studies completed up to 29.10.2012)
- Search in trial registries for studies on dapagliflozin (last search 29.10.2012)
- Bibliographical literature search and search in trial registries for studies on the ACT metformin + sulfonylurea (last search in bibliographical databases 23.10.2012, and in trial registries 24.10.2012)

Combination therapy of dapagliflozin and insulin (coding D)

Sources of the company in the dossier:

- Study list on dapagliflozin in combination with insulin (studies completed up to 29.10.2012)
- Search in trial registries for studies on dapagliflozin (last search 29.10.2012)

Summary

No relevant study was identified for any of the 4 subindications considered by the company (codings A to D) from the steps of information retrieval mentioned. The Institute therefore dispensed with checking the completeness of the study pool presented by the company.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Modules 4A-D, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

2.3.1.1 Dapagliflozin monotherapy (coding A)

No relevant study was identified from the steps of information retrieval mentioned. The data presented by the company were unsuitable for assessing the added benefit of dapagliflozin monotherapy in comparison with the ACT specified. The reasons for this are given below.

Direct comparisons

The company did not present any direct comparative study on dapagliflozin monotherapy versus the ACT (sulfonylureas [glibenclamide or glimepiride]). However, the company presented 2 placebo-controlled studies (MB102013 and MB102032). These were unsuitable for assessing the added benefit of dapagliflozin monotherapy versus the ACT, and were therefore not included in this benefit assessment. This concurred with the approach of the company, which also did not derive conclusions on the added benefit from these 2 studies (based on a direct comparison).

Indirect comparisons

The company conducted an adjusted indirect comparison of dapagliflozin versus sulfonylureas (without limitation to the drugs glibenclamide and glimepiride). The company chose placebo or diet as intermediate comparator. On the dapagliflozin side, the company included the placebo-controlled study MB102013. According to the inclusion criteria of this study it could be assumed that the majority of patients enrolled did not have metformin intolerance and therefore did not receive approval-compliant treatment. The same was true for the 5 studies on the sulfonylurea side identified by the company. The results of the studies cannot simply be applied to patients (with metformin intolerance) who receive approval-compliant treatment. The company did not prove the transferability of the results in Module 4A of the dossier. Hence the studies presented for the indirect comparison were unsuitable for drawing conclusions on the added benefit of dapagliflozin in monotherapy versus the ACT, and were therefore not included in this benefit assessment.

2.3.1.2 Combination therapy of dapagliflozin and metformin (coding B)

No relevant study was identified from the steps of information retrieval mentioned. The data presented by the company were unsuitable for assessing the added benefit of the combination therapy of dapagliflozin and metformin in comparison with the ACT specified. The reasons for this are given below.

Direct comparisons

The company did not present any direct comparative studies on the combination therapy of dapagliflozin and metformin versus the ACT (sulfonylurea [glibenclamide or glimepiride] + metformin). The only study the company included in the assessment, study D1690C00004, conducted a comparison of the combination of metformin and dapagliflozin versus metformin and glipizide. However, glipizide has no longer been approved in Germany since 2007, and is therefore unsuitable as ACT. The key reason the company gave for including this study is the equivalence of glipizide with glimepiride or glibenclamide. The data presented by the company were insufficient to support this statement, however. The study D1690C00004 was therefore unsuitable for a direct comparison versus the ACT (see Section 2.2 and the benefit assessment of the fixed combination of saxagliptin and metformin [4]).

2.3.1.3 Combination therapy of dapagliflozin and sulfonylureas (coding C)

No relevant study was identified from the steps of information retrieval mentioned. The data presented by the company were unsuitable for assessing the added benefit of the combination therapy of dapagliflozin and sulfonylureas in comparison with the ACT specified. The reasons for this are given below.

Direct comparisons

The company did not present any direct comparative studies on the combination therapy of dapagliflozin and sulfonylureas versus the ACT (metformin + sulfonylureas [glibenclamide or glimepiride]). However, the company presented the placebo-controlled study D1690C00005, which compared glimepiride + dapagliflozin treatment with glimepiride + placebo treatment. This study was unsuitable for assessing the added benefit of dapagliflozin in combination with sulfonylureas versus the ACT, and was therefore not included in this benefit assessment. This concurred with the approach of the company, which also did not derive conclusions on the added benefit from this study (based on a direct comparison).

Indirect comparisons

The company conducted an adjusted indirect comparison of dapagliflozin + sulfonylureas versus metformin + sulfonylureas (without limitation to the drugs glibenclamide and glimepiride). The company chose sulfonylureas + placebo as intermediate comparator. On the dapagliflozin side, the company included the study D1690C00005, which compared treatment with glimepiride + dapagliflozin with administration of glimepiride + placebo. The study concurred with the inclusion and exclusion criteria and was therefore, in principle, suitable for an indirect comparison versus the ACT using the intermediate comparator "sulfonylurea + placebo". The 2 studies identified by the company on the comparator side (DeFronzo 1995 [7] and Goldstein 2003 [8]) were not relevant for the research question, however. According to the specifications in the study protocol, all patients in the study of DeFronzo 1995 received a glibenclamide dose of 20 mg/day (equivalent to 15 mg/day of the micronized form used in Germany). A change of this dosage during the course of the study was not envisaged. This dose considerably exceeds the maximal dose of 10.5 mg/day approved in Germany [9]. In the study Goldstein 2003, the sulfonylurea glipizide, which is not approved in Germany, was used. In addition, the study duration (18 weeks) did not meet the inclusion criterion of a minimal study duration of 24 weeks. Hence an indirect comparison versus the ACT cannot be conducted based on the available data.

2.3.1.4 Combination therapy of dapagliflozin and insulin (coding D)

No relevant study was identified from the steps of information retrieval mentioned. The data presented by the company were unsuitable for assessing the added benefit of the combination therapy of dapagliflozin and insulin in comparison with the ACT specified. The reasons for this are given below.

The company presented 3 randomized placebo-controlled trials on the subindication "dapagliflozin in combination with insulin" (D1690C00006, D1690C00018 and D1690C00019), to derive an added benefit.

All 3 studies were unsuitable for assessing the added benefit because, in the comparator groups, it was largely prohibited to adapt the insulin therapy to individual requirements. Patients who received insulin and up to 2 additional oral antidiabetics and did not achieve sufficient glycaemic control under this therapy were enrolled in the placebo-controlled study D1690C00006. D1690C00018 and D1690C00019 were placebo-controlled studies with patients who did not achieve sufficient glycaemic control under prior antidiabetic treatment (with and without insulin). Patients in both treatment arms in all 3 studies were required to continue their prior treatment with insulin (with or without oral antidiabetic) unchanged, i.e. it was neither allowed to change the type of insulin nor the type of insulin therapy. Only in the study D1690C00006, it became possible to change regimen almost 1 year after enrolment of the first patient by amendment to the study protocol. However, this was only possible for the second half of the study (from week 25), and only if unexpected hypoglycaemia occurred with high levels of fasting plasma glucose or HbA1c at the same time. The insulin dose could only be increased as an emergency medication in very high levels of fasting plasma glucose or HbA1c, and reduced in an increased risk of hypoglycaemia. Antidiabetic therapy would usually already be optimized in less pronounced fluctuations of blood glucose levels so that hypoglycaemia and hyperglycaemia do not occur in the first place, and not as a reaction to these events.

Because of the lack of opportunities for optimization – particularly in the respective comparator groups – the 3 studies mentioned were unsuitable for drawing conclusions on the added benefit of dapagliflozin in combination with insulin versus the ACT (metformin + human insulin, or human insulin alone for patients for whom metformin is not an option or ineffective).

Moreover, the company used the data of the placebo-controlled studies to form different subpopulations from the study arms, which broke randomization. These analyses were unsuitable for proving an added benefit from a methodological point of view already. You can find more information on this in Section 2.7.2.3.2.4 of the full dossier assessment.

2.3.1.5 Summary

There was no relevant study in the dossier for assessing the added benefit of dapagliflozin versus the respective ACT for any of the 4 subindications considered by the company (codings A to D). This deviated from the company's approach, which included studies for a direct and/or indirect comparison for all subindications.

Further information on the results of the information retrieval and the study pool derived from it can be found in Modules 4A-D, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.4 Results on added benefit

There were no relevant data for any of the subindications considered by the company (codings A to D), neither for a direct comparison, nor for an indirect comparison. Hence the added benefit versus the respective ACT in the 4 subindications considered by the company is not proven.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit for the 4 subindications considered by the company are given below.

The decision on added benefit is made by the G-BA.

2.5.1 Dapagliflozin monotherapy (coding A)

No proof of added benefit of dapagliflozin versus the ACT "sulfonylureas (glibenclamide or glimepiride)" could be derived from the data presented. Hence there are no patient groups either, for whom a therapeutically important added benefit could be derived.

This assessment deviates from that of the company, which derived an indication of a minor added benefit of dapagliflozin versus sulfonylureas (without limitation to the drugs glibenclamide and glimepiride). Furthermore, the company claimed an indication of a minor added benefit versus the alternative comparator therapy DDP-4 inhibitors for patients for whom sulfonylureas are not an option and in whom insulin is not yet indicated.

2.5.2 Combination therapy of dapagliflozin and metformin (coding B)

No proof of added benefit of the combination therapy of dapagliflozin and metformin versus the ACT "sulfonylureas (glibenclamide or glimepiride) + metformin" could be derived from the data presented. Hence there are no patient groups either, for whom a therapeutically important added benefit could be derived.

This assessment deviates from that of the company, which derived an indication of a considerable added benefit of the combination of dapagliflozin and metformin versus metformin + sulfonylureas (without limitation to the drugs glibenclamide and glimepiride). Furthermore, the company derived a hint of a minor added benefit versus the alternative comparator therapy (metformin + DDP-4 inhibitors) for the patient population it had defined for whom sulfonylureas are not an option and in whom insulin is not yet indicated.

2.5.3 Combination therapy of dapagliflozin and sulfonylureas (coding C)

No proof of added benefit of dapagliflozin in combination with sulfonylureas versus the ACT "metformin + sulfonylureas (glibenclamide or glimepiride)" could be derived from the data presented. There is also no proof of added benefit of dapagliflozin in combination with sulfonylureas versus the ACT "human insulin (if applicable, in combination with

sulfonylureas)" for patients with metformin intolerance. Hence there are no patient groups either, for whom a therapeutically important added benefit could be derived.

This assessment deviates from that of the company, which derived an indication of a minor added benefit of dapagliflozin versus metformin + sulfonylureas (without limitation to the drugs glibenclamide and glimepiride). Furthermore, the company determined an indication of a minor added benefit versus the alternative comparator therapy (sulfonylureas + DDP-4 inhibitors) for patients for whom metformin is not an option and in whom insulin is not yet indicated.

2.5.4 Combination therapy of dapagliflozin and insulin (coding D)

No proof of added benefit of dapagliflozin in combination with insulin versus the ACT (human insulin + metformin, or human insulin alone for patients in whom metformin is not sufficiently effective or is not tolerated) could be derived from the data presented. Hence there are no patient groups either, for whom a therapeutically important added benefit could be derived.

This assessment deviates from that of the company, which derived proof of a minor added benefit for patients treated with dapagliflozin in combination with insulin and 1 or 2 oral antidiabetics versus therapy with metformin + insulin. The company derived an indication of a minor added benefit for patients treated with dapagliflozin in combination with insulin alone versus the ACT.

Further information about the extent and probability of the added benefit can be found in Modules 4A-D, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

Not applicable as the company did not present any relevant studies in its dossier for the 4 subindications considered by the company (codings A to D), from which an added benefit of dapagliflozin versus the respective ACT could be derived.

References for English extract

Please see full dossier assessment for full reference list.

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