Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Dapagliflozin (Reassessment Because of New Scientific Knowledge (Type 2 Diabetes Mellitus))

of 19 December 2019

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

After the active ingredient dapagliflozin (Forxiga®) was first placed on the market on 15 December 2012, the G-BA carried out a benefit assessment of this active ingredient according to Section 35a SGB V. In its resolution of 6 June 2013, as a result of the benefit assessment of the active ingredient dapagliflozin in accordance with Section 35a, paragraph 1, sentence 5 SGB V, the G-BA established that an additional benefit for dapagliflozin compared with the appropriate comparator therapy specified by the G-BA is not proven in all patient groups.

With the resolution of 21 June 2018, the G-BA carried out a renewed benefit assessment according to Section 35a SGB V for the dual combination therapy of dapagliflozin with metformin for the treatment of type 2 diabetes mellitus based on new scientific findings (“DapaZu” study) and found that for dapagliflozin in dual combination therapy with metformin, an additional benefit compared with the appropriate comparator therapy defined by the G-BA is not proven.

In a letter dated 21 January 2019, the pharmaceutical company submitted an application for a renewed benefit assessment for the entire therapeutic indication of dapagliflozin in accordance with Chapter 5, Section 14 of the Rules of Procedure of the G-BA (VerfO). In its session on 7 March 2019, the G-BA decided to grant the application of the pharmaceutical company for a renewed benefit assessment according to Section 35a, paragraph 5 SGB V.

The granting of the application was linked to the condition that the renewed benefit assessment be carried out on the basis of a data basis corresponding to the current generally accepted state of medical and scientific knowledge, including the DECLARE-TIMI 58 Study.

With the resolutions of 7 March 2019, the pharmaceutical company was requested to submit the evidence required for the benefit assessment according to Section 35a, paragraph 1, sentence 3 SGB V within the time limit indicated as requested by the G-BA.

The pharmaceutical company submitted the final dossier to the G-BA in due time in accordance with Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 4 VerfO on 18 June 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 October 2019, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of dapagliflozin compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of dapagliflozin.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of dapagliflozin (Forxiga®) in accordance with product information (July 2019)

"Forxiga is indicated in adults for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1."

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance

a1) in patients without high cardiovascular risk[2]

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

[2] In the present case, high cardiovascular risk is defined according to the DECLARE-TIMI 58 Study (see study protocol, Wiviott et. al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380(4):347–357. DOI: 10.1056/NEJMoa1812389) and summarised here approximately as ≥ 40 years with at least

Appropriate comparator therapy:

- Sulphonylurea (glibenclamide or glimepiride)

a2) in patients at high cardiovascular risk[2] receiving further medication for the treatment of cardiovascular risk factors[3]

Appropriate comparator therapy:

- Sulphonylurea (glibenclamide or glimepiride)

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment <u>with one</u> other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar

b1) in patients without high cardiovascular risk[2]

Appropriate comparator therapy:

- Metformin + sulphonylurea (glibenclamide or glimepiride) or
- Metformin + empagliflozin

b2) in patients at high cardiovascular risk[2] receiving further medication for the treatment of cardiovascular risk factors[3]

Appropriate comparator therapy:

- Metformin + sulphonylurea (glibenclamide or glimepiride) or
- Metformin + empagliflozin or
- Metformin + liraglutide[4]

c) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment <u>with at least two</u> hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

c1) in patients without high cardiovascular risk[2]

Appropriate comparator therapy:

- Human insulin + metformin or
- Only human insulin if metformin is intolerable or contraindicated in accordance with the product information or is not sufficiently effective because of advanced type 2 diabetes mellitus

c2) in patients at high cardiovascular risk[2] receiving further medication for the treatment of cardiovascular risk factors[3]

Appropriate comparator therapy:

---

one cardiovascular disease (ischaemic heart disease, cerebrovascular disease, or peripheral arterial occlusive disease) or women ≥ 60 years and men ≥ 55 years with at least one risk factor for cardiovascular disease (dyslipidemia, hypertension, current smoking with ≥ 5 cigarettes/day for at least one year at the time of randomisation)

[3] In particular anti-hypertensive agents, anticoagulants, and/or lipid-lowering agents

[4] Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive agents, anticoagulants, and/or lipid-lowering agents (for the operationalisation, see study protocols: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–28. DOI 10.1056/NEJMoa1504720 or Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375: 311–322. DOI: 10.1056/NEJMoa1603827).

- Human insulin + metformin or
- Human insulin + empagliflozin[4] or
- Human insulin + liraglutide[4] or
- Human insulin if the particular combination partners in accordance with the product information are incompatible or contraindicated or not sufficiently effective because of an advanced type 2 diabetes mellitus

d) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

d1) in patients without high cardiovascular risk[2]

Appropriate comparator therapy:

- The optimisation of the human insulin regime (possibly + metformin)

d2) in patients at high cardiovascular risk[2] receiving further medication for the treatment of cardiovascular risk factors[3]

Appropriate comparator therapy:

- The optimisation of the human insulin regimen (possibly + metformin *or* empagliflozin[4] *or* liraglutide[4])

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication:

Metformin, sulphonylureas, and insulin (human insulin, insulin analogues) are approved for the mono- and the combination therapy. Marketing authorisations for mono- as well as for the combination therapy also exist for other anti-diabetic agents, among other things alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (gliptine), glinide, SGLT-2 inhibitors (gliflozine) and incretin mimetics.

On 2. A non-medicinal treatment is not deemed applicable as a comparator therapy in this therapeutic indication.

On 3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.

- Linagliptin (resolution of 21 February 2013: An additional benefit is deemed not to have been proven; for the combination with metformin, the additional benefit is not proven; resolution of 16 May 2013 (new therapeutic indication): An additional benefit is deemed not to have been proven),
- Dapagliflozin (resolution of 6 June 2013: An additional benefit is not proven), resolution of 21 June 2018 (reassessment because of new scientific knowledge related exclusively to the dual combination therapy with metformin): An additional benefit is not proven),
- Lixisenatide (resolution of 5 September 2013: An additional benefit is not proven; for the combination with oral anti-diabetic agents, the additional benefit is deemed not to have been proven),
- Saxagliptin/metformin (resolution of 1 October 2013: An additional benefit is not proven),
- Vildagliptin (resolution of 1 October 2013: An additional benefit is not proven; resolution of 21 May 2015: An additional benefit is not proven),
- Vildagliptin/metformin (resolution of 1 October 2013: An additional benefit is not proven),
- Dapagliflozin/metformin (resolution of 7 August 2014: An additional benefit is not proven), resolution of 21 June 2018 (reassessment because of new scientific knowledge related exclusively to the dual combination therapy dapagliflozin/metformin): An additional benefit is not proven)),
- Canagliflozin (resolution of 4 September 2014: An additional benefit is not proven),
- Insulin degludec (resolution of 16 October 2014: An additional benefit is not proven; resolution of 4 December 2014 (new therapeutic indication): An additional benefit is deemed not to have been proven); resolution of 20 August 2015 (new therapeutic indication): An additional benefit is not proven; resolution of 16 May 2019 (reassessment because of new scientific knowledge related exclusively to the treatment of adult patients with type 2 diabetes mellitus): An additional benefit is not proven).
- Canagliflozin/metformin (resolution of 5 February 2015: An additional benefit is not proven),
- Albiglutide (resolution of 19 March 2015: Indication for a minor additional benefit for the combination with metformin; for other treatment regimens, the additional benefit is not proven),
- Dulaglutide (resolution of 16 July 2015: Hint for a minor additional benefit for the combination with insulin (with or without oral anti-diabetic agent); otherwise, the additional benefit is not proven),
- Insulin degludec/liraglutide (resolution of 15 October 2015: An additional benefit is not proven; resolution of 4 February 2016 (new therapeutic indication): An additional benefit is not proven).
- Empagliflozin (resolution of 1 September 2016: For patients with manifest cardiovascular disease in combination with further medication for the treatment of

cardiovascular risk factors, indication for a considerable additional benefit for the combination with one or several hypoglycaemic agents; for patients without manifest cardiovascular disease, hint for a minor additional benefit for the combination with metformin; for all other patient groups, the additional benefit is not proven),

- Empagliflozin/metformin (resolution of 1 September 2016: An additional benefit is not proven).
- Saxagliptin (resolution of 15 December 2016: An additional benefit is not proven).
- Saxagliptin/metformin (resolution of 15 December 2016: An additional benefit is not proven), resolution of 1 February 2018 (new therapeutic indication): An additional benefit is not proven).
- Sitagliptin (resolution of 15 December 2016: Hint for a minor additional benefit for the combination with metformin; for all further patient groups, the additional benefit is not proven; resolution of 22 March 2019 (new benefit assessment after expiry of deadline related exclusively to the dual combination therapy with metformin): Hint for a minor additional benefit).
- Sitagliptin/metformin (resolution of 15 December 2016: An additional benefit is not proven).
- Insulin glargin/lixisenatide (resolution of 16 August 2018: An additional benefit is not proven).
- Ertugliflozin/sitagliptin (resolution of 1 November 2018: An additional benefit is not proven).
- Semaglutide (resolution of 2 May 2019: For patients with manifest cardiovascular disease in combination with further medication for the treatment of cardiovascular risk factors, hint for a minor additional benefit for the combination with one or several hypoglycaemic agents; for all other patient groups, the additional benefit is not proven).

On 4. Metformin is a first-choice oral anti-diabetic agent with proven reduction of overall mortality and heart attack risk[5,6]. For human insulin, a reduction of diabetes-related microvascular complications is proven[7].

Against the background of the proven benefit by influencing patient-relevant endpoints such as subsequent micro- or macrovascular complications, according to the generally recognised state of medical knowledge, metformin as well as sulphonylureas and insulin are to be regarded as appropriate therapies in the therapeutic indication. The sulphonylureas glibenclamide or glimepiride, which are classified by the G-BA as equivalent for the determination of the appropriate comparator therapy, may be considered. Glipizide is pharmacologically and therapeutically comparable with glimepiride in the group of sulphonylureas and is therefore accepted as a comparator in studies in accordance with previous resolutions in the field of type 2 diabetes mellitus.

For empagliflozin in the dual combination with metformin, positive study results are available from Study 1245.28 and the EMPA-REG-Outcome Study regarding cardiovascular endpoints of empagliflozin for patients with type 2 diabetes mellitus

[5] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352(9131): 854–865.
[6] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359(15):1577–1589.
[7] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131): 837–853

exclusively with manifest cardiovascular disease. For the dual combination of empagliflozin with metformin, a hint for a minor additional benefit was found for all patients with type 2 diabetes mellitus compared with the appropriate comparator therapy metformin in combination with sulphonylurea (glimepiride). Furthermore, based on the EMPA-REG-Outcome Study, there was a hint for a considerable additional benefit of empagliflozin in combination with additional medication for the treatment of cardiovascular risk factors for the combination with one or more hypoglycaemic agents for patients with manifest cardiovascular disease. Based on these results, empagliflozin was therefore only named as part of the appropriate comparator therapy for patients with manifest cardiovascular disease. A manifest cardiovascular disease in this regard was operationalised in accordance with inclusion criteria of the EMPA-REG Outcome Study as at least one of the following conditions: confirmed myocardial infarction, clinically-relevant coronary one-vessel disease with ≥ 50% stenosis, coronary multi-vessel disease, unstable angina pectoris with angiographic evidence of a cardiac disorder, ischaemic or haemorrhagic stroke, or peripheral arterial occlusive disease with clinically relevant ischaemia; see study protocol, Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–28. DOI: 10.1056/ NEJMoa1504720.

In addition, for liraglutide, the Rapid Report of the IQWiG on the cardiovascular long-term study LEADER is available. Based on these positive study results in cardiovascular endpoints, the G-BA concluded that liraglutide in addition to at least one other hypoglycaemic agent for patients with type 2 diabetes mellitus with manifest cardiovascular disease and further medication for the treatment of cardiovascular risk factors[8] is to be regarded as appropriate. A manifest cardiovascular disease was operationalised in this regard in accordance with inclusion criteria of the LEADER Study as at least one of the following conditions: confirmed myocardial infarction, confirmed stroke or transient ischaemic attack, clinically relevant arterial occlusive disease or revascularisation, coronary heart disease, confirmed unstable angina pectoris, chronic renal insufficiency (eGFR ≤ 60 ml/min/1.73 m^2) or chronic cardiac insufficiency (NYHA class II or III), see study protocol, Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375: 311–322. DOI: 10.1056/NEJMoa1603827.

There has previously been a lack of long-term safety data on the further approved active ingredients or groups of active ingredients in the therapeutic indication; these are therefore not taken into account as appropriate comparator therapy in the current assessment procedure.

The continuation of an insufficient therapy (scheme) for the treatment of type 2 diabetes mellitus does not correspond to the appropriate comparator therapy.

It is assumed that anti-diabetic therapy is initially started with metformin monotherapy. If metformin is not suitable because of contraindications/incompatibility, a sulphonylurea should be used.

For patient group “b)” *(Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment <u>with one</u> other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar)*, human insulin may be used as a therapeutic option in individual cases in patients for whom metformin is intolerable or contraindicated in accordance with the product information. Because this is a small patient group overall, no separate appropriate comparator therapy is determined.

[8] In particular anti-hypertensive agents, anticoagulants, and/or lipid-lowering agents.

On patient group “c)” *(Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar)*: A multiple combination with three or more hypoglycaemic active ingredients is critically discussed because of its poor controllability and an increased risk for medicinal products interactions and side effects so that in this therapeutic situation, insulin therapy may be indicated in combination with metformin, with empagliflozin[4], or with liraglutide[4]. If metformin, empagliflozin,[4] and liraglutide[4] are incompatible or contraindicated in accordance with the product information or are not sufficiently effective because of an advanced type 2 diabetes mellitus and a combination with insulin is not deemed applicable, human insulin alone is the appropriate comparator therapy.

In the anti-diabetic therapy situation of patient group “d)” *(Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar)* the administration of an additional blood hypoglycaemic agent is not regularly considered to be indicated in the context of an ICT.

It is assumed that for the treatment of co-morbidities in patients with type 2 diabetes mellitus (e.g. hypertonia, dyslipoproteinemias, and coronary artery disease) an individual patient-based treatment of the respective co-morbidities corresponding to the state of medical knowledge, in particular through anti-hypertensive agents, anticoagulants and/or lipid-lowering agents, taking into account the specific characteristics of type 2 diabetes mellitus, will be carried out.

For insulin analogues, according to the generally acknowledged level of medical knowledge, there is neither an advantage nor a disadvantage compared with human insulin; however, long-term data with advantages concerning hard endpoints on insulin analogues is available. In the benefit assessment, evidence from studies in which insulin analogues were used are also taken into account if the transferability of the results from studies with human insulin analogues is established. The marketing authorisation status of the insulin analogues must be taken into account. Study results must be examined for possible effect modifications resulting from the type of insulins used if the studies were carried out with both human insulin and insulin analogues.
However, in the cost comparison, the treatment costs for human insulin must be taken into account because this was designated as an appropriate comparator therapy.

Although insulin glargin is an insulin analogue that was not explicitly named as part of the appropriate comparator therapy, it is nevertheless accepted as suitable comparator taking into account the current data basis.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of dapagliflozin is assessed as follows:

a) Adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance

a1) in patients without high cardiovascular risk[9]

An additional benefit is not proven.

a2) in patients at high cardiovascular risk[9] receiving further medication for the treatment of cardiovascular risk factors[10]

An additional benefit is not proven.

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar

b1) in patients without high cardiovascular risk[9]

An additional benefit is not proven.

b2) in patients at high cardiovascular risk[9] receiving further medication for the treatment of cardiovascular risk factors[10]

Hint for a minor additional benefit

c) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

c1) in patients without high cardiovascular risk[9]

An additional benefit is not proven.

c2) in patients at high cardiovascular risk[9] receiving further medication for the treatment of cardiovascular risk factors[10]

Hint for a minor additional benefit

d) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

d1) in patients without high cardiovascular risk[9]

An additional benefit is not proven.

d2) in patients at high cardiovascular risk[9] receiving further medication for the treatment of cardiovascular risk factors[10]

Hint for a minor additional benefit

Justification:

Cross-patient aspects

[9] In the present case, high cardiovascular risk is defined according to the DECLARE-TIMI 58 Study (see study protocol, Wiviott et. al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380(4):347–357. DOI: 10.1056/NEJMoa1812389) and summarised here approximately as ≥ 40 years with at least one cardiovascular disease (ischaemic heart disease, cerebrovascular disease, or peripheral arterial occlusive disease) or women ≥ 60 years and men ≥ 55 years with at least one risk factor for cardiovascular disease (dyslipidemia, hypertension, current smoking with ≥ 5 cigarettes/day for at least one year at the time of randomisation)

[10] In particular anti-hypertensive agents, anticoagulants, and/or lipid-lowering agents

Adult patients with type 2 diabetes mellitus without high cardiovascular risk

To prove the additional benefit for the renewed benefit assessment according to Section 35a SGB V of dapagliflozin for the entire approved therapeutic indication for the treatment of insufficiently controlled type 2 diabetes mellitus in adults, the pharmaceutical company has submitted the DECLARE-TIMI 58 Study. In the DECLARE-TIMI 58 Study, only patients with a high cardiovascular risk[9] were examined.

Data for patients without high cardiovascular risk, which are also included in the approved therapeutic indication for dapagliflozin, were not provided in the dossier of the pharmaceutical company. In its written statement, the pharmaceutical company subsequently submitted a literature search for studies with dapagliflozin compared with the appropriate comparator therapy and does not identify any studies suitable for early benefit assessment. At the oral hearing, the pharmaceutical company also stated that there are no studies suitable for early benefit assessment that would allow a comparison of dapagliflozin with the comparator therapy specified by the G-BA in adult patients with type 2 diabetes mellitus who do not have a high cardiovascular risk. For these patient populations, the studies presented by the pharmaceutical company have already been evaluated in the previous procedures for early benefit assessment. Therefore, the additional benefit of dapagliflozin compared with the appropriate comparator therapy has not been proven for patients without high cardiovascular risk in the present therapeutic indication – patient groups a1), b1), c1), and d1).

Adult patients with type 2 diabetes mellitus with high cardiovascular risk[9] DECLARE-TIMI 58 Study

For the renewed benefit assessment of dapagliflozin according to Section 35a SGB V, the DECLARE-TIMI 58 Study is available for both monotherapy and combination therapy in patients with type 2 diabetes mellitus and high cardiovascular risk.

Patients with different previous treatments were included in the study. The study medication in the intervention or comparator arm was given in addition to a “standard therapy” of type 2 diabetes mellitus and other cardiovascular risk factors and comorbidities. Because of the design of the DECLARE-TIMI 58 Study, the total population includes patients with different comparative therapies. These cannot be divided into the different patient populations in accordance with the specifications of the G-BA for the corresponding patient groups a2), b2), c2), and d2) as well as the respective appropriate comparison therapy options defined. The documents submitted subsequently in connection with the statement procedure were also not suitable for differentiating between the patient groups. Therefore, an assessment of the DECLARE-TIMI 58 Study can only be made across all patients for patient groups a2), b2), c2), and d2) together.

The DECLARE-TIMI 58 Study is a randomised, double blind, placebo controlled two-arm study, which was carried out in multiple centres in Africa, Asia, Australia, Europe, and North and South America. The DECLARE-TIMI 58 Study included adult patients aged ≥ 40 years with type 2 diabetes mellitus with an HbA1c value in the range of ≥ 6.5% and < 12% who had a high cardiovascular risk. A high cardiovascular risk was defined as follows.
Patients with a minimum age of 40 years had to have a **manifest cardiovascular disease** with at least one of the following criteria: ischaemic heart disease (documented by previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, or ≥ 50% stenosis in at least 2 coronary arteries), peripheral vascular disease (documented by previous treatment of the peripheral arteries, amputation of the lower extremities because of peripheral arterial occlusive disease, or existing symptoms of intermittent claudication in combination with an ankle-arm index < 0.90 within the last 12 months), or cerebrovascular disease (documented by previous stroke, carotid stenting, or endarterectomy).

Women with a minimum age of 60 years and men with a minimum age of 55 years had to have at least **one risk factor for cardiovascular disease** with at least one of the following criteria: Dyslipidemia (documented by an LDL-C value > 130 mg/dl within the last 12 months or by a lipid-lowering therapy prescribed by a doctor in the context of hypercholesterolemia with confirmed documentation of an LDL-C value > 130 mg/dl), hypertension (documented by elevated systolic blood pressure [> 140 mmHg] and elevated diastolic blood pressure [> 90 mmHg] at study enrolment or by doctor-prescribed anti-hypertensive therapy), or current smoking (≥ 5 cigarettes/day for at least 1 year at the time of randomisation). Approximately 60% of patients had at least one risk factor for cardiovascular disease without manifest cardiovascular disease; the most common risk factor was hypertension. The remaining 40% of patients had manifest cardiovascular disease; the majority of these had ischaemic heart disease.

The patient characteristics were balanced between the treatment groups: the patients were 64 years old on average; they were predominantly male (62%); about 44% of the study participants can be assigned to the region Europe. At the start of study, the average HbA1c value was 8.3%, and systolic blood pressure was 135 mmHg. The average diabetes duration was 12 years.

A total of 17,160 patients were allocated to the treatment arms dapagliflozin 10 mg (N = 8,582) or placebo (N = 8,587) at a ratio of 1:1; each of the treatments was administered in addition to the existing anti-diabetic treatment and cardiovascular background therapy. Almost all patients (98%) received anti-diabetic therapy at the start of study; about 41% were treated with insulin (possibly in combination with oral anti-diabetics), about 81% with metformin, and more than 40% with sulphonylurea. More than 80% of the study participants were given at least one cardiovascular concomitant treatment with anti-hypertensives, lipid-lowering agents, and/or antithetical medication at the start of study.

To achieve the glycaemic targets[11] recommended by the American Diabetes Association ADA and European Association for the Study of Diabetes EASD, anti-diabetic background therapy should be adjusted at the investigator's discretion and according to local guidelines and standards. Treatment with another SGLT-2 inhibitor, among others, was not allowed at any time during the study. According to the study protocol, a patient-individual HbA1c value of < 7.0% should be targeted. Less stringent target values were planned for some patients (e.g. those with a history of severe hypoglycaemia). The therapy of cardiovascular risk factors should also be performed in accordance with local standards.

The primary endpoint of the study was the combined endpoint MACE, consisting of cardiovascular death, myocardial infarction, and stroke. As of Amendment 5, a combined endpoint consisting of hospitalisation because of cardiac failure and cardiovascular death was collected as an additional primary endpoint. Further morbidity endpoints regarding the progression of kidney disease were identified. Endpoints on health-related quality of life were not investigated.

The study duration was planned to be event-driven until at least 1,390 patients with a confirmed serious cardiovascular event (MACE) were recorded. The median observation period was 4.2 years in both treatment arms. Patients who discontinued the study medication prematurely after randomisation were monitored until the end of study.

[11] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M. Management of Hyperglycaemia in Type 2 Diabetes: A Patient-Centred Approach. Diabetes Care 2012; 35: 1364–1379

Implementation of the appropriate comparator therapy

In accordance with the study protocol, blinded investigators should adjust the anti-diabetic medication to achieve optimal glycaemic control on a patient-individual basis in accordance with the therapy recommendations. This applied from the start of study and later at any time during the entire duration of the study. The administration of other SGLT-2 inhibitors was not permitted during the blinded phase; this is due to the design of the DECLARE-TIMI 58 study. Because of the blinding, it would have been possible for the patients in the intervention arm to receive another SGLT-2 inhibitor in addition to dapagliflozin if the exclusion for other SGLT-2 inhibitors (e.g. empagliflozin) had not existed. On the other hand, the use of GLP-1-RA (e.g. liraglutide) was permitted throughout the course of the study if the treating investigators considered it to be indicated. According to this, concomitant therapy with GLP-1-RA was newly initiated in approx. 9% of patients in the intervention arm and 11% in the control arm.

After the start of study, approx. 49% of the patients in the intervention arm and approx. 54% of the patients in the comparator arm received insulin therapy. Considering the proportion of patients who started insulin therapy during the study in relation to those patients who did not receive insulin therapy at the start of study, the following is observed: at 22.6% in the comparator arm compared with 12.1% in the intervention arm, almost twice as many insulin-dependent patients in the control group started a new insulin therapy in the course of the study compared with the dapagliflozin group.

In terms of therapy optimisation (e.g. by starting an additional anti-diabetic therapy for at least three months during the study) this occurred in a significantly higher proportion of patients in the comparator arm compared with the intervention arm (50% vs 35%, respectively).

With regard to the mean change in the HbA1c value during the course of the DECLARE-TIMI 58 Study, an average reduction in the HbA1c value from 8.3% at the start of study to 7.9% and 8.1% after 4 years in the intervention arm and comparator arm, respectively, was achieved despite the progressive course of the disease. Thus, at least the HbA1c values are approximately in the target ranges. According to the guidelines[12], these are to be expected in elderly patients with long-term diabetes, in patients with severe comorbidities and a history of severe hypoglycaemia, or in patients with advanced cardiovascular disease. According to a recent guideline[12] of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD), target HbA1c levels in these patients are in the range < 8% or ≤ 9%. Nevertheless, for a part of the patients, especially those for whom the ESC/EASD guideline recommends a target HbA1c value of < 7.0%, no sufficient reduction in HbA1c values was achieved.

In view of the adjustments made in anti-diabetic therapy in the course of the DECLARE-TIMI 58 Study through the additional administration of (further) hypoglycaemic agents to ensure optimal glycaemic control for each individual patient, it can be assumed that the patients were predominantly treated according to the recommendations of the applicable guidelines or regional clinical practice. Against this background and because the study investigated endpoints for cardiovascular safety in the treatment of type 2 diabetes mellitus patients, the DECLARE-TIMI 58 Study is used for the early benefit assessment.

On the results of the study:

[12] Cosentino et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European Heart Journal (2019) 00, 1 – 69; doi:10.1093/eurheartj/ehz486

Mortality and morbidity

Overall mortality/cardiovascular mortality

There are no statistically significant differences between treatment groups with respect to overall mortality and the endpoint “fatal myocardial infarction” or “fatal stroke”.

Combined endpoint MACE and cardiovascular death

The combined endpoint “Major adverse cardiovascular events (MACE)” includes the endpoints cardiovascular death, myocardial infarction, and stroke. In the combined endpoint MACE and cardiovascular death[13], there are no statistically significant differences between treatment groups.

Cardiac failure

In the combined endpoint cardiac failure, consisting of the individual components “hospitalisation because of cardiac failure” and “severe cardiac failure (SMQ cardiac failure)”, statistically significant differences in favour of dapagliflozin were found in the individual components. However, because of the effect size the extent cannot be considered as more than minor.

Kidney disease

“Kidney disease” is a combined endpoint for complications associated with kidney disease and consists of the following components:

- confirmed sustained ≥ 40% reduction of eGFR to eGFR < 60 ml/min/1.73 m^2 (using CKD-EPI equation)
- End-stage kidney disease consisting of the components:
  - Dialysis ≥ 90 days,
  - Kidney transplant
  - confirmed sustained eGFR < 15 ml/min/1.73 m^2)
- Kidney death.

The single component *“confirmed sustained ≥ 40% reduction of eGFR to eGFR < 60 ml/min/1.73 m^2”* indicates a progressive deterioration of renal function starting from CKD stage 3 (with moderate functional impairment) and including stages 4 and 5 (with severe functional impairment and chronic renal failure). Reaching CKD stage 4 and 5 is patient-relevant. However, there are different opinions in the G-BA on the extent to which CKD stage 3 is classified as patient-relevant. The proportion of patients in the study who have reached CKD stage 3 cannot be estimated.

In the combined endpoint kidney disease as well as for the individual components “confirmed sustained reduction of eGFR” and “end-stage kidney disease”, there was a statistically significant difference in favour of dapagliflozin compared with the control. However, because of the effect size the extent cannot be considered as more than minor.

Other morbidity endpoints

There are no statistically significant differences between the treatment groups for the endpoints “treatment of retinopathy” and “surgical or spontaneous non-surgical amputations”.

Quality of life

In the DECLARE-TIMI 58 Study, no endpoints in the quality of life category were collected.

[13] Not shown separately in the resolution

Side effects

Total rates

No data are available on the overall rate of AE because not all AE were fully documented in the study. Only SAE, discontinuations because of AE, and AE of special interest were recorded as per predefined PT collection.

Initially, only evaluations of the overall rate of SAE were presented in the dossier; these were followed up only until 30 days after therapy discontinuation. These evaluations also included results on renal events and renal complications already recorded in the morbidity endpoints. The written statement of the pharmaceutical company presents further evaluations of SAE covering the entire observation period up to the last round and rule out subsequent complications including renal events and retinopathies. These data on the overall rate of SAE show a statistically significant difference to the benefit of dapagliflozin.

For the endpoints “discontinuation because of AE”, there is a statistically significant difference to the disadvantage of dapagliflozin compared with the comparator arm.

Specific AE

For the endpoint bladder cancer, there is a statistically significant difference in favour of dapagliflozin. For the endpoint “definitive diabetic ketoacidosis”, on the other hand, there is a statistically significant difference to the disadvantage of dapagliflozin compared with the comparator arm.

For the endpoints “breast cancer”, “prostate cancer”, “probable or possible diabetic ketoacidosis”, and “symptoms of volume deficiency”, there are no statistically significant differences between the treatment arms.

Additional key points

HbA1c

At the start of study, patients in both study arms had an average HbA1c value of 8.3%. By month 48, the HbA1c level in patients in the dapagliflozin arm was reduced by 0.4%; in patients in the comparator arm, the level was reduced by 0.2%. The differences between the treatment arms are statistically significant. The endpoint “HbA1c” is a surrogate parameter and not per se patient-relevant.

Body weight

At the start of study, patients in both treatment arms weighed approx. 91 kg on average. By month 48, the body weight in the dapagliflozin arm was reduced by 3.5 kg on average; in the comparator arm, it was reduced by 1.6 kg. The differences between the treatment arms are statistically significant. The endpoint “Body weight” is a surrogate parameter and not per se patient-relevant.

<u>On the individual treatment regimens:</u>

a) Adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance

a1) in patients without high cardiovascular risk[14]

An additional benefit is not proven.

Justification:

No study was presented compared with the appropriate comparator therapy (sulphonylurea: glibenclamide or glimepiride) that would have been appropriate to evaluate the additional benefit of dapagliflozin monotherapy for the treatment of adult patients without high cardiovascular risk with inadequately controlled type 2 diabetes mellitus in addition to diet and exercise if the application of metformin is considered unsuitable because of intolerance.

a2) in patients at high cardiovascular risk[14] receiving further medication for the treatment of cardiovascular risk factors[15]

An additional benefit is not proven.

Justification:

No study was presented compared with the appropriate comparator therapy (sulphonylurea: glibenclamide or glimepiride) that would have been appropriate to evaluate the additional benefit of dapagliflozin monotherapy for the treatment of adult patients with high cardiovascular risk[9] with inadequately controlled type 2 diabetes mellitus in addition to diet and exercise if the application of metformin is considered unsuitable because of intolerance.

In the DECLARE-TIMI 58 Study presented for an assessment of the additional benefit in patients with high cardiovascular risk[9] in combination with additional medication for the treatment of cardiovascular risk factors[9], only 1.9% of patients were treated with dapagliflozin without further anti-diabetic medication. In addition, it is unclear to what extent the authorisation criterion “metformin intolerance if diet and exercise alone do not sufficiently control blood glucose” has been taken into account for these patients or how large the proportion of patients is. Consequently, no meaningful data can be derived from this study to assess the additional benefit of dapagliflozin in (anti-diabetic) monotherapy in patients with high cardiovascular risk[9] if diet and exercise alone do not adequately control blood glucose and the use of metformin is considered unsuitable because of intolerance.

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar

b1) in patients without high cardiovascular risk[14]

An additional benefit is not proven.

Justification:

No study has been presented in comparison to the appropriate comparator therapy (metformin in combination with sulphonylurea or with empagliflozin) that would have been suitable to evaluate the additional benefit of dapagliflozin in combination therapy with another hypoglycaemic agent (other than insulin) in adult patients without high cardiovascular risk[9] with

[14] In the present case, high cardiovascular risk is defined according to the DECLARE-TIMI 58 Study (see study protocol, Wiviott et. al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380(4):347–357. DOI: 10.1056/NEJMoa1812389) and summarised here approximately as ≥ 40 years with at least one cardiovascular disease (ischaemic heart disease, cerebrovascular disease, or peripheral arterial occlusive disease) or women ≥ 60 years and men ≥ 55 years with at least one risk factor for cardiovascular disease (dyslipidemia, hypertension, current smoking with ≥ 5 cigarettes/day for at least one year at the time of randomisation)

[15] In particular anti-hypertensive agents, anticoagulants, and/or lipid-lowering agents

inadequately controlled type 2 diabetes mellitus if treatment with another blood glucose-lowering drug (other than insulin) in addition to diet and exercise does not adequately control blood glucose.

b2) in patients at high cardiovascular risk[14] in combination with further medication for the treatment of cardiovascular risk factors[15]

Hint for a minor additional benefit

Justification:

See the comments on cross-patient group aspects, p. 10 ff.

c) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

c1) in patients without high cardiovascular risk[14]

An additional benefit is not proven.

Justification:

There are no studies available compared with the appropriate comparative therapy (human insulin in combination with metformin) that would have been appropriate to assess the additional benefit of dapagliflozin in combination therapy with at least two hypoglycaemic agents (except insulin) in adult patients without high cardiovascular risk[9] with inadequately controlled type 2 diabetes mellitus if treatment with at least two hypoglycaemic agents (except insulin) in addition to diet and exercise does not adequately control blood glucose.

c2) in patients at high cardiovascular risk[14] in combination with further medication for the treatment of cardiovascular risk factors[15]

Hint for a minor additional benefit

Justification:

See the comments on cross-patient group aspects, p. 10 ff.

d) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

d1) in patients without high cardiovascular risk[14]

An additional benefit is not proven.

Justification:

There are no studies available compared with the appropriate comparative therapy (optimisation of the human insulin regime, *possible* + *metformin*) that would have been appropriate to assess the additional benefit of dapagliflozin in combination therapy with insulin in adult patients without high cardiovascular risk[9] with inadequately controlled type 2 diabetes mellitus if treatment insulin (with or without another hypoglycaemic agent) in addition to diet and exercise does not adequately control blood glucose.

d2) in patients at high cardiovascular risk[14] in combination with further medication for the treatment of cardiovascular risk factors[15]

Hint for a minor additional benefit

Justification:

See the comments on cross-patient group aspects, p. 10 ff.

Overall assessment

The DECLARE-TIMI 58 Study was presented for a renewed benefit assessment according to Section 35a SGB V based on new scientific findings of dapagliflozin as a monotherapy or in combination with other anti-diabetics for the treatment of inadequately controlled type 2 diabetes mellitus in addition to diet and exercise in adults. Based on the data presented, statements can only be made for patients with type 2 diabetes mellitus with a high cardiovascular risk. For patients without high cardiovascular risk, there are no suitable studies available for comparison with the appropriate comparator therapy.

The study investigated dapagliflozin versus placebo, in each case, in addition to a standard therapy defined as a patient-individual background therapy for the treatment of type 2 diabetes mellitus and other cardiovascular risk factors and comorbidities according to relevant guidelines. Overall, it can be assumed that the patients were predominantly treated according to guideline recommendations and that the anti-diabetic treatment carried out as part of the standard therapy is at least a sufficient approximation to the appropriate comparator therapy of the respective patient groups.

The aim of the study was to demonstrate the cardiovascular safety of dapagliflozin measured by the combined endpoint of *major adverse cardiovascular event* (MACE) as well as the additional primary combined endpoint consisting of hospitalisation for cardiac failure and cardiovascular death.

In the category of mortality and morbidity for the endpoint “MACE” (cardiovascular death, myocardial infarction, or ischaemic stroke) and “cardiovascular death”, there are no statistically significant differences between treatment groups.

In the morbidity category, statistically significant differences in favour of dapagliflozin were shown in the endpoints “hospitalisation because of cardiac failure” and “severe cardiac failure (SMQ cardiac failure)” as well as in the combined endpoint for kidney disease and in the individual components “confirmed sustained ≥ 40% reduction in eGFR” and “end-stage kidney disease”. However, because of the effect size the extent cannot be considered as more than minor.

Endpoints for the quality of life category were not collected in the study.

In the side effects category, there is a statistically significant difference between the overall rate of SAE and the specific AE bladder cancer in favour of treatment with dapagliflozin. In contrast, dapagliflozin has a statistically significant disadvantage in the endpoints “therapy discontinuation because of AE” and in the specific AE “definitive diabetic ketoacidosis (DKA)”.

In the overall view of the results, the extent of the additional benefit is considered to be minor.

For patients without high cardiovascular risk, the additional benefit is not proven.

Reliability of data (probability of additional benefit)

For the benefit assessment of dapagliflozin for the entire approved therapeutic indication, only the DECLARE-TIMI 58 Study is available. This study exclusively examines type 2 diabetes mellitus patients from the age of 40 years with a high cardiovascular risk[9].
The study shows uncertainties that limit the significance of the results. Thus, statistically significant differences in HbA1 values were found between the treatment arms in the course of the study. For example, the HbA1c value was at least 0.2–0.6% higher than the intervention arm. The average HbA1c value was consistently in the range of about 8.2% in the comparator arm and about 7.6% to 7.9% in the dapagliflozin arm. This suggests that the therapy intensification carried out in the study, especially in the comparator arm, was not sufficient. The positive effects in the morbidity endpoints of cardiac failure and kidney disease can

therefore only be interpreted to a limited extent. In addition, the therapeutic goal of a mean HbA1c value of < 7.0%, if adequate for individual patients, was not achieved overall in the study.
As a result, there was inadequate blood glucose control for a portion of the treated patients in the study, especially those for whom the ESC/EASD guideline recommends a target HbA1c level of below 7.0%. This contributes to the uncertainties that the therapy intensification carried out could have been further optimised, especially in the comparator arm.

Overall, therefore, the reliability of data is classified in the “hint” category.

2.1.4 Summary of the assessment

The present evaluation is a renewed benefit assessment of the medicinal product Forxiga® containing the active ingredient dapagliflozin, which is indicated as monotherapy or in addition to other anti-diabetic agents for the treatment of inadequately controlled type 2 diabetes mellitus in adult patients as a supplement to diet and exercise.

In the present case, the entire approved therapeutic indication is considered. Four patient groups were distinguished; these were then each divided into two further subgroups.

a) Adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance,

   a1) in patients without high cardiovascular risk[16]

   a2) in patients at high cardiovascular risk[16] receiving further medication for the treatment of cardiovascular risk factors[17]

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar

   b1) in patients without high cardiovascular risk[16]

   b2) in patients at high cardiovascular risk[16] receiving further medication for the treatment of cardiovascular risk factors[17]

c) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

   c1) in patients without high cardiovascular risk[16]

   c2) in patients at high cardiovascular risk[16] receiving further medication for the treatment of cardiovascular risk factors[17]

[16] In the present case, high cardiovascular risk is defined according to the DECLARE-TIMI 58 Study (see study protocol, Wiviott et. al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380(4):347–357. DOI: 10.1056/NEJMoa1812389) and summarised here approximately as ≥ 40 years with at least one cardiovascular disease (ischaemic heart disease, cerebrovascular disease, or peripheral arterial occlusive disease) or women ≥ 60 years and men ≥ 55 years with at least one risk factor for cardiovascular disease (dyslipidemia, hypertension, current smoking with ≥ 5 cigarettes/day for at least one year at the time of randomisation)
[17] In particular anti-hypertensive agents, anticoagulants, and/or lipid-lowering agents

d) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

d1) in patients without high cardiovascular risk[16]

d2) in patients at high cardiovascular risk[16] receiving further medication for the treatment of cardiovascular risk factors[17]

Patient group a1)

Sulphonylurea (glibenclamide or glimepiride) was determined as an appropriate comparator therapy by the G-BA.

There is no study available. In the overall picture, the additional benefit of dapagliflozin as monotherapy compared with the appropriate comparator therapy is not proven for this patient group.

Patient group a2)

Sulphonylurea (glibenclamide or glimepiride) was determined as an appropriate comparator therapy by the G-BA.

The randomised, double-blind, placebo-controlled, two-arm DECLARE-TIMI 58 Study was presented. In this study, patients with inadequately controlled type 2 diabetes mellitus and a manifest cardiovascular disease or at least one risk factor for cardiovascular disease were examined. The administration of dapagliflozin was compared with placebo, in each case in addition to a "standard therapy" of type 2 diabetes mellitus and other cardiovascular risk factors and comorbidities.

In the study, only 1.9% of patients were treated with dapagliflozin without further anti-diabetic therapy. It is also unclear to what extent or how large the proportion of patients is in which the authorisation criterion "metformin intolerance" was taken into account.

In the overall picture, the additional benefit of dapagliflozin as monotherapy compared with the appropriate comparator therapy is not proven for this patient group.

Patient group b1)

The following therapies were determined as an appropriate comparator therapy by the G-BA:

- Metformin + sulphonylurea (glibenclamide or glimepiride) or
- Metformin + empagliflozin

There is no study available. In the overall picture, the additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy is not proven for this patient group.

Patient group b2)

The following therapies were determined as an appropriate comparator therapy by the G-BA:

- Metformin + sulphonylurea (glibenclamide or glimepiride) or
- Metformin + empagliflozin or
- Metformin + liraglutide[18]

The randomised, double-blind, placebo-controlled, two-arm DECLARE-TIMI 58 Study was presented. In this study, patients with inadequately controlled type 2 diabetes mellitus and a manifest cardiovascular disease or at least one risk factor for cardiovascular disease were

[18] Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive agents, anticoagulants, and/or lipid-lowering agents (for the operationalisation, see study protocols: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–28. DOI 10.1056/NEJMoa1504720 or Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375: 311–322. DOI: 10.1056/NEJMoa1603827).

examined. The administration of dapagliflozin was compared with placebo, in each case in addition to a “standard therapy” of type 2 diabetes mellitus and other cardiovascular risk factors and comorbidities.

Overall, it can be assumed that the patients were predominantly treated according to the recommendations of the applicable guidelines or regional clinical practice. The study for this patient group is therefore used for the early benefit assessment.

In the category morbidity in the endpoints “hospitalisation because of cardiac failure”, “severe cardiac failure (SMQ cardiac failure)”, in the combined endpoint regarding kidney disease or in the individual components “confirmed sustained 40% reduction in eGFR” and “end-stage kidney disease”, and in the category adverse events in the endpoints “overall rate of SAE” and the specific AE “bladder cancer”, statistically significant differences in favour of dapagliflozin are shown. In contrast, the endpoints “therapy discontinuation because of AE and the specific AE “definitive diabetic ketoacidosis (DKA)” each show a statistically significant difference to the disadvantage of dapagliflozin. For the remaining endpoints, no statistically significant differences between the treatment arms can be identified. Endpoints for the quality of life category were not collected in the study.

Against the background that the therapy intensification carried out could have been further optimised, especially in the comparator arm, the study as a whole is subject to uncertainties.

Overall, in this patient group, a hint for a minor additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy can be derived.

Patient group c1)

The following therapies were determined as an appropriate comparator therapy by the G-BA:

- Human insulin + metformin or
- Only human insulin if metformin is intolerable or contraindicated in accordance with the product information or is not sufficiently effective because of advanced type 2 diabetes mellitus

There is no study available. In the overall picture, the additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy is not proven for this patient group.

Patient group c2)

The following therapies were determined as an appropriate comparator therapy by the G-BA:

- Human insulin + metformin or
- Human insulin + empagliflozin[18] or
- Human insulin + liraglutide[18] or
- Human insulin if the particular combination partners in accordance with the product information are incompatible or contraindicated or not sufficiently effective because of an advanced type 2 diabetes mellitus

The randomised, double-blind, placebo-controlled, two-arm DECLARE-TIMI 58 Study was presented. In this study, patients with inadequately controlled type 2 diabetes mellitus and a manifest cardiovascular disease or at least one risk factor for cardiovascular disease were examined. The administration of dapagliflozin was compared with placebo, in each case in addition to a “standard therapy” of type 2 diabetes mellitus and other cardiovascular risk factors and comorbidities.

Overall, it can be assumed that the patients were predominantly treated according to the recommendations of the applicable guidelines or regional clinical practice. The study for this patient group is therefore used for the early benefit assessment.

In the category morbidity in the endpoints “hospitalisation because of cardiac failure”, “severe cardiac failure (SMQ cardiac failure)”, in the combined endpoint regarding kidney disease or in the individual components “confirmed sustained 40% reduction in eGFR” and “end-stage kidney disease”, and in the category adverse events in the endpoints “overall rate of SAE” and the specific AE “bladder cancer”, statistically significant differences in favour of dapagliflozin

are shown. In contrast, the endpoints “therapy discontinuation because of AE and the specific AE “definitive diabetic ketoacidosis (DKA)” each show a statistically significant difference to the disadvantage of dapagliflozin. For the remaining endpoints, no statistically significant differences between the treatment arms can be identified. Endpoints for the quality of life category were not collected in the study.

Against the background that the therapy intensification carried out could have been further optimised, especially in the comparator arm, the study as a whole is subject to uncertainties.

Overall, in this patient group, a hint for a minor additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy can be derived.

Patient group d1)

The following therapies were determined as an appropriate comparator therapy by the G-BA:

- The optimisation of the human insulin regime (possibly + metformin)

There is no study available. In the overall picture, the additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy is not proven for this patient group.

Patient group d2)

The following therapies were determined as an appropriate comparator therapy by the G-BA:

- The optimisation of the human insulin regimen (possibly + metformin *or* empagliflozin[18] *or* liraglutide[18])

The randomised, double-blind, placebo-controlled, two-arm DECLARE-TIMI 58 Study was presented. In this study, patients with inadequately controlled type 2 diabetes mellitus and a manifest cardiovascular disease or at least one risk factor for cardiovascular disease were examined. The administration of dapagliflozin was compared with placebo, in each case in addition to a “standard therapy” of type 2 diabetes mellitus and other cardiovascular risk factors and comorbidities.

Overall, it can be assumed that the patients were predominantly treated according to the recommendations of the applicable guidelines or regional clinical practice. The study for this patient group is therefore used for the early benefit assessment.

In the category morbidity in the endpoints “hospitalisation because of cardiac failure”, “severe cardiac failure (SMQ cardiac failure)”, in the combined endpoint regarding kidney disease or in the individual components “confirmed sustained 40% reduction in eGFR” and “end-stage kidney disease”, and in the category adverse events in the endpoints “overall rate of SAE” and the specific AE “bladder cancer”, statistically significant differences in favour of dapagliflozin are shown. In contrast, the endpoints “therapy discontinuation because of AE and the specific AE “definitive diabetic ketoacidosis (DKA)” each show a statistically significant difference to the disadvantage of dapagliflozin. For the remaining endpoints, no statistically significant differences between the treatment arms can be identified. Endpoints for the quality of life category were not collected in the study.

Against the background that the therapy intensification carried out could have been further optimised, especially in the comparator arm, the study as a whole is subject to uncertainties.

Overall, in this patient group, a hint for a minor additional benefit of dapagliflozin in combination with other anti-diabetics compared with the appropriate comparator therapy can be derived.

2.2 Number of patients or demarcation of patient groups eligible for treatment

This information on the number of patients concerns the target population in the statutory health insurance.

The data basis concerning the published literature on the current prevalence and incidence of diabetes mellitus in Germany is restricted and heterogeneous despite the significance of the disease.

The G-BA takes into account the data from the IQWiG working paper on the determination of the SHI target population for the indication type 2 diabetes mellitus in the corresponding therapeutic situations in accordance with the third validation level (https://www.iqwig.de/download/GA16-03_Routinedaten-bei-Diabetes-mellitus-Typ-2_Arbeitspapier_V1-1.pdf *[Accessed 12 December 2019]*). The figures given in the working paper refer to the data year 2013. Because of the increasing prevalence in the indication type 2 diabetes mellitus, the target population could include more patients in 2019.

The patient numbers considered include patients with validated (i.e. repeated) prescriptions of an active ingredient within the year under consideration. Hereby, all patients newly treated with anti-diabetics and those who did not receive a second prescription of an active ingredient within the year under review are not included in the 4th quarter of the year under review. This aspect may also lead to an underestimation of the number of patients in the target population.

Starting treatment with dapagliflozin is not recommended for patients over 75 years of age. However, no age restriction is taken into account in the patient numbers available. Furthermore, according to the product information, there are restrictions on use in patients with kidney dysfunction. These patients were also not reported separately. However, because the information in the working paper is based on real medicinal product prescriptions, it can be assumed that existing restrictions of the therapeutic indication were taken into account in the corresponding prescriptions by the doctors. However, it cannot be ruled out that the figures given also include patients who are not eligible for treatment with dapagliflozin.

Because there is a lack of follow-up observations on the basis of which conclusions can be drawn about the prescription consequences of anti-diabetics in the course of the disease, a proportion of patients in patient group c) *(patients in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar)* is used to determine the number of patients in the next therapy stage. This corresponds to the guideline recommendations in this therapy situation that basal-supported oral therapy (BOT) may also be indicated in these patients. In principle, patients receiving monotherapy with basal insulin or monotherapy with bolus insulin are also considered.
Overall, patient group c) includes patients with a triple or multiple combination of anti-diabetics (except insulin) on one hand and patients receiving BOT, basal insulin monotherapy, and bolus insulin monotherapy on the other.

When determining the number of patients in patient group d) (patients in whom diet and movement and the treatment (with or without another anti-diabetic agent) do not sufficiently control the blood sugar), on the one hand, dual combinations of insulin and another anti-diabetic agent (here: metformin, sulfonylurea, another anti-diabetic agent) are considered. These dual combinations include all possible types of insulin therapy (basal, bolus, CT, ICT, other insulin combinations). On the other hand, this patient group also includes those patients who receive monotherapy with insulin as part of CT, ICT, and other insulin combinations (except monotherapy with basal insulin or bolus insulin). Because patients receiving a dual combination of basal insulin and another anti-diabetic agent as part of a BOT are also included in patient group c), a possible overestimation of patient numbers cannot be ruled out.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of

product characteristics, SmPC) for Forxiga® (active ingredient: dapagliflozin) at the following publicly accessible link (last access: 13 November 2019):

https://www.ema.europa.eu/documents/product-information/forxiga-epar-product-information_de.pdf

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 2019).

Treatment duration and consumption

Concerning the usage and consumption, the average annual consumption was calculated by indicating the number of tablets or individual doses. The daily doses recommended in the product information were used as the calculation basis and, if required, corresponding margins were formed. The separate description of possibly required titration phases was dispensed with because the anti-diabetic therapy is a continuous long-term therapy, and the titration is performed in a patient-individual manner.

The data on the treatment duration and the dosage was taken from the corresponding product information.

The recommended dose of dapagliflozin as mono- or combination therapy is 10 mg once daily.

For metformin, initial dosages of 500 mg or 850 mg two to three times daily are recommended, but dose increases to up to 3,000 mg metformin daily are possible; the overall dose is generally allocated to 2–3 doses. The cost representation is therefore based on a potency of 1,000 mg metformin/tablet.

Therapy with glibenclamide should be started with 1.75–3.5 mg and increased to up to 10.5 mg glibenclamide per day if the metabolism is insufficient. The calculation is based on a potency of 3.5 mg because this dosage can cover all dosages recommended in the product information.

Therapy with glimepiride in combination with other oral anti-diabetics should be started with a low initial dose and gradually increased to the maximum tolerated daily dose depending on the targeted metabolic status. The recommended maximum dose is 6 mg; however, according to the product information, doses of glimepiride above 4 mg per day improve the effect only in isolated cases.

For empagliflozin, an initial dosage of 10 mg once daily as combination therapy with other hypoglycaemic agents including insulin is recommended. If there is insufficient metabolic control, the dose can be increased to 25 mg once daily. Therefore, both potencies are taken into account for the cost representation.

The daily initial dose of liraglutide is 0.6 mg; after one week, this is increased to 1.2 mg. According to the product information, patients can possibly benefit from a further increase of the dose from 1.2 mg to 1.8 mg. The corresponding dose of liraglutide is injected subcutaneously every day (single-use pen).

For the insulin therapy, a large number of various insulin dosage schemes is possible. In addition, in accordance with the insulin dosage scheme used, the quantity of insulin and the application frequency must be coordinated individually according to the patient's physical activity and lifestyle. In order to guarantee a comparability of the costs, simplified assumptions have been made for the presentation of the treatment duration and dosage. In the table "Treatment duration", the mode of treatment for human insulin (NPH insulin or premixed

insulin) is represented as “1–2 × daily” even if the application frequency can deviate in some patients. According to the product information[19], the average insulin requirement is often 0.5–1.0 I.U. per kg body weight per day. The basal daily insulin requirement is generally 40–60% of the daily insulin requirement; the remaining requirement is covered through mealtime-dependent bolus insulin. The calculation of bolus insulin consumption is based on three main meals. The calculation of the dose of insulin per day was based on this data.

In principle, the G-BA does not base the calculation of the consumption of weight-dependent medicinal products to be dispensed on indication-specific average weights. Therefore, for the body weight, a mean body weight of 77.0 kg according to the official representative statistic “Microcensus 2017” is assumed[20].

Consequently, weight differences between women and men as well as the fact that body weight in patients with type 2 diabetes mellitus can lie above the mean value of 77.0 kg are not taken into account for the cost calculation.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Patient population a), b), c), and d)				
Dapagliflozin	continuously, 1 × daily	365	1	365
Patient population b)				
+ metformin or	continuously, 2–3 × daily	365	1	365
+ glibenclamide or + glimepiride	continuously, 1–2 × daily continuously, 1 × daily	365 365	1 1	365 365
Patient population c)				
+ metformin	continuously, 2–3 × daily	365	1	365
+ glibenclamide or + glimepiride	continuously, 1–2 × daily continuously, 1 × daily	365 365	1 1	365 365

[19] Product information on Insuman® Basal, last revised: April 2019.

[20] German Federal Office for Statistics, Wiesbaden, 2 August 2018. Microcensus 2017: Fragen zur Gesundheit; Körpermaße der Bevölkerung 2017 [Questions about health; body measurements of the 2017 population] [online]. [Access: 1 November 2019] https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Patient population d)				
+ human insulin (NPH insulin)	continuously, 1–2 × daily	365	1	365
possibly + metformin	continuously, 2–3 × daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
Glibenclamide or	continuously, 1–2 × daily	365	1	365
Glimepiride	continuously, 1 × daily	365	1	365
Patient population b)				
Metformin	continuously, 2–3 × daily	365	1	365
Glibenclamide or	continuously, 1–2 × daily	365	1	365
Glimepiride	continuously, 1 × daily	365	1	365
Empagliflozin	continuously, 1 × daily	365	1	365
Liraglutide	continuously, 1 × daily	365	1	365
Patient population c)				
Human insulin (NPH insulin)	continuously, 1–2 × daily	365	1	365
Metformin	continuously, 2–3 × daily	365	1	365
Empagliflozin	continuously, 1 × daily	365	1	365
Liraglutide	continuously, 1 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
<u>Conventional insulin therapy</u> Premixed insulin	continuously, 1–2 × daily	365	1	365
Patient population d)				
<u>Intensified conventional insulin therapy</u> Human insulin (bolus insulin)	continuously, 3 × daily	365	1	365
Human insulin (NPH insulin)	continuously, 1–2 × daily	365	1	365
<u>Conventional insulin therapy</u> Premixed insulin	continuously, 1–2 × daily	365	1	365
possibly + metformin	continuously, 2–3 × daily	365	1	365
possibly + empagliflozin	continuously, 1 × daily	365	1	365
possibly + liraglutide	continuously, 1 × daily	365	1	365

<u>Usage and consumption:</u>

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Patient populations a), b), c), and d)					
Dapagliflozin	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
Patient populations b), c), and d)					

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
+ metformin hydrochloride	500 mg	1000 mg –	1 × 1,000 mg –	365	365 × 1,000 mg
	1,000 mg	3,000 mg	3 × 1,000 mg		1095 × 1,000 mg
Patient populations b) and c)					
+ glibenclamide or	1.75 mg	1.75 mg	1/2 × 3.5 mg	365	182.5 × 3.5 mg
	7 mg/3.5 mg	10.5 mg	3 × 3.5 mg		1095 × 3.5 mg
+ glimepiride	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg
	6 mg	6 mg	1 × 6 mg		365 × 6 mg
Patient population d)					
+ human insulin (NPH)	0.5	38.5	1 × 38.5 I.U.	365	14,052.5 I.U.
	1 I.U. per kg/BW	77 I.U.	1 × 77 I.U.	365	28,105 I.U.
Appropriate comparator therapy					
Patient population a)					
Glibenclamide	1.75 mg	1.75 mg	1/2 × 3.5 mg	365	182.5 × 3.5 mg
	7 mg/3.5 mg	10.5 mg	3 × 3.5 mg		1095 × 3.5 mg
Glimepiride	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg
	6 mg	6 mg	1 × 6 mg		365 × 6 mg
Patient population b)					
Metformin	500 mg	1,000 mg –	1 × 1,000 mg –	365	365 × 1,000 mg
	1,000 mg	3,000 mg	3 × 1,000 mg		1095 × 1,000 mg

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
+ glibenclamide	1.75 mg	1.75 mg	1/2 × 3.5 mg	365	182.5 × 3.5 mg
or	7 mg/3.5 mg	10.5 mg	3 × 3.5 mg		1095 × 3.5 mg
+ glimepiride	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg -
or	6 mg	6 mg	1 × 6 mg		365 × 6 mg
+ empagliflozin	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
or	25 mg	25 mg	1 × 25 mg		365 × 25 mg
+ liraglutide[21]	1.2 mg	1.2 mg	1 × 1.2 mg	365	365 × 1.2 mg
or	1.8 mg	1.8 mg	1 × 1.8 mg		365 × 1.8 mg
Patient population c)					
Human insulin (NPH)	0.5	38.5	1 × 38.5 I.U.	365	14052.5 I.U.
	1 I.U. per kg/BW	77 I.U.	1 × 77 I.U.		28,105 I.U.
+ metformin or	500 mg	1,000 mg –	1 × 1,000 mg –	365	365 × 1,000 mg
	1,000 mg	3,000 mg	3 × 1,000 mg		1095 × 1,000 mg
+ empagliflozin	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
or	25 mg	25 mg	1 × 25 mg		365 × 25 mg
+ liraglutide[21]	1.2 mg	1.2 mg	1 × 1.2 mg	365	365 × 1.2 mg

[21] In accordance with the product information, each single-use contains 18 mg of liraglutide in 3 ml of solution; this corresponds to 10–15 single doses. Packages with 2, 5, and 10 single-use pens are available.

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
or	1.8 mg	1.8 mg	1 × 1.8 mg		365 × 1.8 mg
Conventional insulin therapy Premixed insulin	0.5 – 1 I.U. per kg/BW	38.5 – 77 I.U.	1 × 38.5 I.U. - 1 × 77 I.U.	365	14,052.5 I.U. - 28,105 I.U.
Patient population d)					
Intensified conventional insulin therapy[22] Human insulin (NPH insulin) +	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 - 1 × 46.2 I.U.	365	5,621 I.U. - 16,863 I.U.
Human insulin (bolus insulin)	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 - 1 × 46.2 I.U.	365	5,621 I.U. - 16,863 I.U.
Conventional insulin therapy Premixed insulin	0.5 – 1 I.U. per kg/BW	38.5 – 77 I.U.	1 × 38.5 I.U. - 1 × 77 I.U.	365	14,052.5 I.U. - 28,105 I.U.

[22] 40–60% of the daily insulin requirement is generally covered through basal insulin; average insulin requirement: 0.5–1.0 I.U./kg body weight/day; reference: 77 kg body weight (“Microcensus 2017”); in addition, fast-acting insulin (bolus insulin) is given at main mealtimes.

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
possibly + metformin	500 mg	1,000 mg	1 × 1,000 mg	365	365 × 1,000 mg
	1,000 mg	3,000 mg	3 × 1,000 mg		1095 × 1,000 mg
possibly + empagliflozin	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
	25 mg	25 mg	1 × 25 mg		365 × 25 mg
possibly + liraglutide[21]	1.2 mg	1.2 mg	1 × 1.2 mg	365	365 × 1.2 mg
	1.8 mg	1.8 mg	1 × 1.8 mg		365 × 1.8 mg

Costs:

Costs of the medicinal product:

The calculation of the treatment costs for the active ingredients metformin, gilbenclamide and glimepiride, human insulin and premixed insulin was based on the fixed reimbursement rate in each case.

For the calculation of medicinal product costs, the required number of packs according to potency was first determined on the basis of consumption. The medicinal product costs were calculated with the calculated number of required packs, based on the costs per packs, after deduction of the statutory rebate. In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Section 130a SGB V (paragraph 1, 1a, 3a) and Section 130, paragraph 1 SGB V.

In the case of a conventional insulin therapy, the costs were based on the costs for premixed insulin (i.e. a human insulin preparation in a certain premixing ratio of 30% normal insulin to 70% basal insulin).

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Dapagliflozin	98 FCT	€ 103.40	€ 1.77	€ 5.12	€ 96.51
possibly + metformin[23] 1,000 mg	180 FCT	€ 18.78	€ 1.77	€ 0.62	€ 16.39
possibly + glibenclamide[23] 3.5 mg	180 TAB	€ 14.93	€ 1.77	€ 0.31	€ 12.85
possibly + glimepiride 1 mg[23]	180 TAB	€ 16.87	€ 1.77	€ 0.47	€ 14.63
possibly + glimepiride 6 mg[23]	180 TAB	€ 82.53	€ 1.77	€ 5.66	€ 75.10
possibly + human insulin (NPH insulin)[23]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Appropriate comparator therapy					
Empagliflozin 10 mg	100 FCT	€ 192.34	€ 1.77	€ 10.04	€ 180.53
Empagliflozin 25 mg	100 FCT	€ 192.34	€ 1.77	€ 10.04	€ 180.53
Glibenclamide[23] 3.5 mg	180 TAB	€ 14.93	€ 1.77	€ 0.31	€ 12.85
Glimepiride 1 mg[23]	180 TAB	€ 16.87	€ 1.77	€ 0.47	€ 14.63
Glimepiride 6 mg[23]	180 TAB	€ 82.53	€ 1.77	€ 5.66	€ 75.10
Human insulin (bolus insulin)[23]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Human insulin (NPH insulin)[23]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Metformin[23] 1,000 mg	180 FCT	€ 18.78	€ 1.77	€ 0.62	€ 16.39
Premixed insulin[23]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Liraglutide 18 mg	100 – 150 SD	€ 570.64	€ 1.77	€ 30.99	€ 537.88
Abbreviations: SD = single doses; FCT = film-coated tablets, I.U. = International Units; TAB = Tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 December 2019

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product or package information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

It is assumed that blood glucose self-monitoring is carried out 1–3 times a day when the

[23] Fixed reimbursement rate

metabolic status is stable. Because of the selective contractual agreements on blood glucose test strips, lancets, and disposable needles, the corresponding costs are charged on the basis of the cheapest pack in each case and shown on the basis of the pharmacy retail price level.

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/package[24]	Number	Consumption/year
Medicinal product to be assessed (dapagliflozin in combination with insulin (with or without oral anti-diabetic agent))				
Human insulin (NPH insulin)	Blood sugar test strips	€ 18.50	1–3 × daily	365–1,095
	Lancets	€ 4.10	1–3 × daily	365–1,095
	Disposable needles	€ 16.90	1–2 × daily	365–730
Appropriate comparator therapy				
Human insulin (NPH insulin) as well as Conventional insulin therapy (premixed insulin)	Blood sugar test strips	€ 18.50	1–3 × daily	365–1,095
	Lancets	€ 4.10	1–3 × daily	365–1,095
	Disposable needles	€ 16.90	1–2 × daily	365–730
Intensified conventional insulin therapy	Blood sugar test strips	€ 18.50	4–6 × daily	1,460–2,190
	Lancets	€ 4.10	4–6 × daily	1,460–2,190
	Disposable needles	€ 16.90	4–5 × daily	1,460–1,825
Liraglutide	Disposable needles	€ 16.90	1 × daily	365

Other services covered by SHI funds: none

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

[24] Number of blood glucose test strips/pack = 50 pc; number of lancets/pack = 200 pc; number of disposable needles/pack = 100 pc; representation of the cheapest pack in accordance with LAUER-TAXE®, last revised: 1 December 2019.

4. Process sequence

On 18 June 2019, the pharmaceutical company submitted a dossier for the benefit assessment of dapagliflozin to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, Number 4 VerfO.

By letter dated 18 June 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient dapagliflozin.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 September 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 October 2019. The deadline for submitting written statements was 22 October 2019.

The oral hearing was held on 11 November 2019.

By letter dated 12 November 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 29 November 2019.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 10 December 2019, and the proposed resolution was approved.

At its session on 19 December 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Working group Section 35a	5 November 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	11 November 2019	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 November 2019 3 December 2019	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	10 December 2019	Concluding discussion of the proposed resolution
Plenum	19 December 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 19 December 2019

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken