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 (new therapeutic indication: Type 1 diabetes mellitus)

of 17 October 2019

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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

The active ingredient dapagliflozin was listed for the first time on 15 November 2012 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 20 March 2019, dapagliflozin received the marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 17 April 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient dapagliflozin with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication (adult patients indicated for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy).

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 August 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 comments 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

Forxiga is indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with insufficiently controlled type 1 diabetes mellitus and a BMI ≥ 27 kg/m^2 whose blood sugar is not adequately controlled despite optimal insulin therapy.

Appropriate comparator therapy:

Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin aspart, insulin glulisine, insulin lispro)[2]

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] 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] The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus does not correspond to an appropriate comparator therapy if there is still the option of optimising insulin therapy.

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. Insulins (human insulin, insulin analogues) are authorised for mono- and combination therapy of type 1 diabetes mellitus.

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

On 3. The following resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V exist in the therapeutic indication Type 1 diabetes mellitus in adults:
- Resolution on the benefit assessment according to Section 35a SGB V of 16 October 2014: Insulin degludec.

On 4. For human insulin, a reduction of diabetes-related microvascular complications is proven. However, there are currently no long-term data with advantages with regard to hard endpoints of insulin analogues that prove a preventive effect with regard to microangiopathies. With regard to the lower risk for the occurrence of (nightly) hypoglycaemia, insulin analogues are recommended in addition to human insulin in the S3 guideline “Therapy of type 1 diabetes” as well as in the NICE, ADA, and SIGN guidelines. Against the background of the proven benefit of influencing patient-relevant endpoints such as diabetes-related microvascular complications with human insulin and with respect to the guideline recommendations for insulin analogues regarding the lower risk for (nightly) hypoglycaemia, according to the generally recognised state of medical knowledge, human insulin and insulin analogues (insulin detemir, insulin glargine, insulin aspart, insulin glulisine, and insulin lispro) represent the appropriate comparator therapy in the therapeutic indication in question.

In the case of insufficiently adjusted blood sugar control in the indication type 1 diabetes mellitus, the unchanged continuation of an inadequate therapy does not correspond to an appropriate comparator therapy if there is still the option of optimising insulin therapy.

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:

Hint for a minor additional benefit.

Justification:

DEPICT 1 and DEPICT 2 studies

The DEPICT 1 and DEPICT 2 studies were submitted for the benefit assessment of dapagliflozin in type 1 diabetes mellitus. Both studies have an identical study design (twin studies) and are described jointly below. The double-blind, parallel, randomised, placebo-controlled and multi-centre studies were conducted in Asia, Europe, and South and North America from November 2014 to April 2018. The aim of the studies was to investigate the efficacy and safety of dapagliflozin compared with placebo as an add-on therapy to insulin.

Included were patients aged 18 and over with Type 1 diabetes mellitus who had been treated with insulin for at least 12 months. At the start of treatment, the patients had to have an HbA1c between ≥ 7.5% and ≤ 10.5% as well as a BMI ≥ 18 kg/m^2. The sub-population relevant for the benefit assessment (BMI of ≥ 27 kg/m^2) within the studies corresponds to approx. 58% (N = 299 for DEPICT 1) and approx. 48% (N = 262 for DEPICT 2) of the patients of the total population.

8 weeks before randomisation, the patients received an optimisation of insulin treatment to improve their diabetes control (lead-in phase). The insulin treatment was optimised at the doctor's discretion based on the blood glucose values measured by the patient as well as in accordance with the patient's individual needs and local guidelines. Patients who had been hospitalised for hypoglycaemia or severe hypoglycaemia in the month prior to the start of study were excluded from the DEPICT 1 and DEPICT 2 studies. At the start of treatment with the study medication (dapagliflozin or placebo), the study protocol recommended a reduction of the insulin dose by up to 20% in order to reduce the initial risk of hypoglycaemia. Insulin reduction was not mandatory, and the timing and extent were at the discretion of the physician. If reduction is achieved, a back titration to the initial dose should be sought under close control. Although a reduction at the start of treatment corresponds to the recommendation in the product information on dapagliflozin, this initially results in inadequate treatment for the comparator arm because the dose was reduced despite optimised insulin therapy. This was taken into account in the endpoint specific assessment of the risk of bias. In the further course of the study, the insulin treatment was adapted and optimised to the individual patient according to the criteria mentioned above.

The duration of treatment in both studies was 52 weeks and was divided into 24-weeks of short-term therapy followed by 28 weeks of long-term therapy.

The primary endpoint in both studies was the change in HbA1c from start of treatment at week 24. Patient-relevant secondary endpoints were overall mortality and morbidity endpoints as well as AEs, including hypoglycaemia and diabetic ketoacidoses (DKAs).

Extent and probability of the additional benefit

Mortality

In both studies, no deaths occurred after 52 weeks. For the endpoint overall mortality, there therefore was no statistically significant difference between the treatment arms.

Morbidity

HbA1c value

The HbA1c value is used to determine the proportion of glycated haemoglobin in the patient's blood. The HbA1c value is regarded as a sufficiently valid surrogate for microvascular secondary diseases in the therapeutic indication type 1 diabetes mellitus.

Dossier 2 presents various operationalisations for the HbA1c value. For the change in the HbA1c value compared with baseline, the meta-analysis reveals a statistically significant difference to the advantage of dapagliflozin and insulin compared with placebo and insulin (MD −0.33% [−0.47; −0.19]; $p < 0.001$).

For the responder analysis HbA1c reduction ≥ 0.5% (RR 1.92 [1.48; 2.50]; $p < 0.001$), the meta-analysis reveals a statistically significant difference to the advantage of dapagliflozin and insulin compared with placebo and insulin.

When considering the mean change in the HbA1c value, an irrelevant group difference cannot be ruled out because the 95% CI of the effect is not completely outside the generally used relevance limit of 0.3 percentage points. However, the direction of the effect is consistent with the results of the responder analysis. Overall, the endpoint HbA1c (as a sufficiently valid surrogate endpoint for microvascular complications) shows an additional benefit of dapagliflozin and insulin compared with insulin.

Health status (EQ-5D VAS)

With the visual analogue scale (VAS) of the EQ-5D, the patients themselves answer the question regarding their health status at the time of the measurement.

For the endpoint general health status measured using the EQ-5D VAS, the meta-analysis reveals a statistically significant difference to the advantage of dapagliflozin and insulin compared with placebo and insulin. However, the 95% CI of the standardised mean difference (Hedges' g) is not completely outside the irrelevance range of −0.2 to 0.2. Thus, it cannot be concluded with sufficient certainty that the effect observed is clinically relevant.

HFS-II (Worry Subscale)

The HFS-II (*Hypoglycemia Fear Survey*) is a questionnaire that records concerns and fears related to hypoglycaemia. The endpoint HFS-II (Worry Subscale) was collected only in the DEPICT 2 study. In the study, there was no statistically significant difference between the treatment arms.

Quality of life

The DEPICT 1 and DEPICT 2 studies did not investigate endpoints of the endpoint category health-related quality of life.

Side effects

Serious adverse events (SAEs)

For the endpoint SAE, the meta-analysis does not reveal any statistically significant difference between dapagliflozin and insulin and placebo and insulin.

Discontinuation because of AEs

The dossier presented contradictory evaluations on the endpoint *Discontinuation because of AEs*, which could only be addressed with information submitted in the written statement procedure. The meta-analysis shows no statistically significant difference between dapagliflozin and insulin compared with placebo and insulin.

symptomatic, confirmed hypoglycaemias

In the meta-analysis for symptomatic, confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dl), a statistically significant difference to the disadvantage of dapagliflozin and insulin was found. This included the incorrectly randomised patients. The sensitivity analysis in the addendum (without incorrectly randomised patients) also shows a statistically significant result. However, for symptomatic, confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dl), no statistically significant result to the advantage or disadvantage of dapagliflozin was found.

Overall, no negative effect can be derived from the results in this endpoint.

Severe hypoglycaemias

For the endpoint severe hypoglycaemia (where medical treatment was given or the patient was treated with glucagon injection or glucose i.v.) there was no statistically significant advantage or disadvantage for dapagliflozin.

Serious hypoglycaemias

For the endpoint serious hypoglycaemias (PT, SAE), the meta-analysis does not reveal any statistically significant difference between dapagliflozin and insulin and placebo and insulin.

Diabetic ketoacidoses

For the endpoint diabetic ketoacidoses (divided into possible or possible + definite), the meta-analysis does not reveal any statistically significant difference between dapagliflozin and insulin and placebo and insulin.

Genital infections and gastrointestinal disorders

For the endpoints genital infections and gastrointestinal disorders (SOC, AE) the meta-analysis reveals a statistically significant difference to the disadvantage of dapagliflozin and insulin compared with placebo and insulin.

Urinary tract infections

For the endpoint urinary tract infections (PT, SAE), the meta-analysis does not reveal any statistically significant difference between dapagliflozin and insulin and placebo and insulin.

Overall assessment/conclusion

For the benefit assessment of dapagliflozin for the new therapeutic indication for the treatment of adult patients with a BMI ≥ 27 kg/m^2 with insufficiently controlled type 1 diabetes mellitus if insulin alone does not sufficiently control blood sugar despite optimal insulin therapy, the two twin studies DEPICT 1 and DEPICT 2 are available. These studies compared the administration of dapagliflozin compared with placebo, each as an adjunctive therapy to insulin. Because of the increased risk of diabetic ketoacidosis in patients with low BMI (below 27 kg/m^2), marketing authorisation was restricted to patients with BMI ≥ 27 kg/m^2[3].

For dapagliflozin, a statistically significant advantage was observed in the morbidity category for the endpoint extent of blood glucose control based on the results of the HbA1c value, which was collected in two different operationalisations. There is a statistically significant advantage in the change in the HbA1c value as well as in the responder analyses (HbA1c reduction by ≥ 0.5 percentage points).

For the endpoint symptomatic, confirmed hypoglycaemia, for the blood sugar limit of ≤ 70 mg/dl, there is difference to the disadvantage of dapagliflozin. However, for symptomatic, confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dl), there was no disadvantage for dapagliflozin. Overall, no negative effect can be derived from the results in this endpoint.

The endpoints genital infections and gastrointestinal disorders (SOC, AE) each show a statistically significant difference to the disadvantage of dapagliflozin compared with the control arm.

For the other endpoints surveyed, there were no statistically significant differences.

In the overall view of the study results, the positive effect of dapagliflozin on the reduction of the valid surrogate endpoint HbA1c value outweighs the disadvantages in the side effects, which is why a minor additional benefit is found for dapagliflozin compared with the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The benefit assessment of dapagliflozin for the treatment of adult patients with a BMI ≥ 27 kg/m^2 with an insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy is based on two randomised, double-blind, and directly comparative studies with identical study designs (DEPICT 1 and DEPICT 2).

The studies included adult patients with type 1 diabetes mellitus with a BMI of ≥ 18 kg/m^2. Only 58% of the patients in the DEPICT 1 study and 48% of the patients in the DEPICT 2 study are relevant for the benefit assessment. These patients correspond to the patient population with a BMI of ≥ 27 kg/m^2, which is compliant with marketing authorisation.

For both DEPICT studies, the cross-endpoint risk of bias is considered low.

Because of a randomisation error in the DEPICT 1 study, the first 55 patients included were excluded from the evaluation of efficacy endpoints but not for the endpoints of the mortality and side effects categories. In the written statement procedure, the pharmaceutical company submitted further evaluations of the results. The addendum of the IQWiG thus lists the results without these patients. The subsequent evaluations allow a better assessment of the submitted data. Nevertheless, residual uncertainties remain.

During an 8-week lead-in phase prior to randomisation, patients received an optimisation of their insulin treatment to improve blood glucose control. Subsequently, a reduction of up to 20% of the insulin dose in both study arms was prescribed at the start of treatment in accordance with the study protocol. Although this is due to the recommendation of the product information for dapagliflozin, it resulted in an initially inadequate treatment of patients in the

[3] EPAR https://www.ema.europa.eu/en/documents/variation-report/edistride-h-c-4161-ws-1344-epar-assessment-report-variation_en.pdf *[Accessed 23 September 2019]*

comparator arm, who had to reduce their insulin dose despite previously optimised insulin therapy. It must therefore be assumed that the results on the HbA1c value are higher in the comparator arm than in everyday care with optimised (insulin) therapy. Therefore, the effect for the endpoint is potentially overestimated. For this reason, the endpoint extent of blood glucose control (in both operationalisations, change in HbA1c and HbA1c reduction ≥ 0.5 percentage points) is considered potentially highly biased. In addition, patients who had been hospitalised for hypoglycaemia or severe hypoglycaemia in the month prior to the start of study were excluded from DEPICT 1 and DEPICT 2 studies. Thus, the results may be biased towards the endpoints hypoglycaemia and reduction of HbA1c.

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

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient dapagliflozin. The therapeutic indication assessed here is as follows:

Adult patients with insufficiently controlled type 1 diabetes mellitus and a BMI ≥ 27 kg/m^2 whose blood sugar is not adequately controlled despite optimal insulin therapy.

Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin aspart, insulin glulisine, and insulin lispro) were determined as appropriate comparator therapies by the G-BA. For this patient group, the pharmaceutical company presents the RCTs DEPICT 1 and DEPICT 2 in which dapagliflozin was compared with placebo (in each case as adjunctive therapy to insulin).

Data on mortality, morbidity, and adverse events are available. In terms of mortality, there was no statistically significant difference between treatment groups.

For dapagliflozin, a statistically significant advantage was observed in the morbidity category for the endpoint extent of blood glucose control based on the results of the HbA1c value, which was collected in two different operationalisations. There is a statistically significant difference in the change in the HbA1c value in favour of dapagliflozin therapy (the relevance of which cannot be conclusively assessed) as well as in the responder analyses (HbA1c reduction by ≥ 0.5 percentage points).

The DEPICT 1 and DEPICT 2 studies did not investigate endpoints of the endpoint category health-related quality of life.

For the total rates of the serious adverse events, there were no statistically significant differences between the treatment arms.

The endpoints genital infections and gastrointestinal disorders show a statistically significant difference to the detriment of patients treated with dapagliflozin.

The interpretation of the morbidity endpoint reduction of HbA1c remains uncertain because of the risk of bias of the initial reduction of the optimised insulin dose as well as the exclusion of patients who had severe hypoglycaemia four weeks prior to the study. Therefore, despite the existence of two studies for the statistically significant difference in this endpoint for dapagliflozin compared with the control, it can be assumed that there is at most one hint for a statistically significant difference.

In the overall view of the study results, the positive effect of dapagliflozin on the reduction of the valid surrogate endpoint HbA1c value outweighs the disadvantages in the side effects, which is why for dapagliflozin in combination with insulin, there is a hint for a minor additional benefit compared with insulin therapy.

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. Especially for sub-populations in the therapy cascade of diabetes therapy, there is a lack of valid published data, which is why some patient numbers can only be estimated.

The G-BA takes into account the patient numbers stated in the dossier and in the opinion of the pharmaceutical company for the present therapeutic indication. However, these are subject to uncertainties because of the limited epidemiological data basis on the incidence and prevalence of diabetes mellitus.

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: 10 September 2019):

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

Treatment with dapagliflozin may only be initiated and monitored by specialists who are experienced in the treatment of patients type 1 diabetes mellitus.

For patients in whom inadequate blood glucose control is associated with severe hypoglycaemia, particularly in the period prior to the planned start of dapagliflozin therapy, the indication for dapagliflozin should be carefully considered.

Before starting the treatment, it should be ensured that the ketone body levels are normal. During the first one to two weeks of treatment with dapagliflozin, the ketone bodies should be monitored regularly. Thereafter, the frequency of ketone body level testing should be individually adjusted according to the patient's lifestyle and/or risk factors.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material. The training material is intended to inform healthcare professionals and patients of the increased risk of ketoacidosis associated with dapagliflozin therapy.

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 October 2019).

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 individually for each patient.

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

For dapagliflozin, the once daily dosage of 5 mg is recommended. Dapagliflozin may only be used as a supplement to insulin.

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) is represented as "1–2 × daily", even if the application frequency can deviate in some patients. According to the product information[4], 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[5].

Consequently, weight differences between women and men and the increased BMI of the patient population are not taken into account in the cost calculation.

[4] Product information on Insuman® Basal, last revised: April 2019.
[5] German Federal Office for Statistics, Wiesbaden, 2 August 2018. Microcensus 2017: Questions on health; body measurements of the population 2017 [online]. [Access: 11 September 2019].

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Dapagliflozin	continuous, 1 × daily	365	1	365
Intensified conventional insulin therapy				
Human insulin (bolus insulin)	continuous, 3 × daily	365	1	365
Human insulin (NPH insulin)	continuous, 1–2 × daily	365	1	365
Appropriate comparator therapy				
Intensified conventional insulin therapy				
Human insulin (bolus insulin)	continuous, 3 × daily	365	1	365
Human insulin (NPH insulin)	continuous, 1–2 × daily	365	1	365
Long-acting insulin analogues				
Insulin detemir	continuous, 1–2 × daily	365	1	365
Insulin glargine	continuous, 1 × daily	365	1	365
possibly plus human insulin (bolus insulin)	continuous, 3 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Rapid acting insulin analogues				
Insulin aspart	continuous, 3 × daily	365	1	365
Insulin glulisine	continuous, 3 × daily	365	1	365
Insulin lispro	continuous, 3 × daily	365	1	365
plus human insulin (NPH insulin))	continuous, 1–2 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Dapagliflozin	5 mg	5 mg	1 × 5 mg	365	365 × 5 mg
Intensified conventional insulin therapy Human insulin (NPH insulin) +	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 I.U. - 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 I.U. - 1 × 46.2 I.U.	365	5,621 I.U. - 16,863 I.U.

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/patient/ year	Annual average consumption by potency
Appropriate comparator therapy					
Intensified conventional insulin therapy[6] Human insulin (NPH insulin) +	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 I.U. - 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 I.U. - 1 × 46.2 I.U.	365	5,621 I.U. - 16,863 I.U.
Long-acting insulin analogues					
Insulin detemir (monotherapy)	0.5 - 1 I.U. per kg/BW	38.5 - 77 I.U.	1 × 38.5 U. - 1 × 77 U.	365	14,052.5 U. - 28,105 U.
Insulin detemir +	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 – 1 × 46.2 U.	365	5,621 U. - 16,863 U.
Human insulin (bolus insulin)	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 I.U. - 1 × 46.2 I.U.	365	5,621 I.U. - 16,863 I.U.
Insulin glargine (monotherapy)	0.5 - 1 I.U. per kg/BW	38.5 - 77 I.U.	1 × 38.5 U. - 1 × 77 U.	365	14,052.5 U. - 28,105 U.

[6]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/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/patient/ year	Annual average consumption by potency
Insulin glargine +	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 U. – 1 × 46.2 U.	365	5,621 U. - 16,863 U.
Human insulin (bolus insulin)	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 I.U.– 1 × 46.2 I.U.	365	5,621 I.U. - 16,863 I.U.
Rapid acting insulin analogues					
Insulin aspart	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 U. – 1 × 46.2 U.	365	5,621 U. - 16,863 U.
Insulin glulisine	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 U. – 1 × 46.2 U.	365	5,621 U. - 16,863 U.
Insulin lispro	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 U. – 1 × 46.2 U.	365	5,621 U. - 16,863 U.
plus human insulin (NPH insulin))	0.2 - 0.6 I.U. per kg/BW	15.4 – 46.2 I.U.	1 × 15.4 I.U.– 1 × 46.2 I.U.	365	5,621 I.U. - 16,863 I.U.

Costs:

Costs of the medicinal product:

The calculation of the treatment costs for human insulin was based on the fixed amount.

To calculate the medicinal product costs, the required number of packs of a particular potency was first determined on the basis of consumption. Based on the determined number of packages required, the medicinal product costs were then calculated based on the costs per package after deduction of the statutory rebates. 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.

For the calculation of the costs of the medicinal products to be evaluated (dapagliflozin + insulin therapy), an ICT was used as an example for insulin therapy. For the calculation of the costs of the appropriate comparator therapy (human insulin or insulin analogues), an ICT was used as an example for insulin therapy. The costs of insulin analogues were calculated either as monotherapy or in combination with human insulin as bolus insulin. Rapid-acting insulin analogues were calculated in combination with human insulin (NPH 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					
Dapagliflozin	28 FCT	€ 37.39	€ 1.77	€ 1.46	€ 34.16
Human insulin (bolus insulin)[7]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Human insulin (NPH insulin)[7]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Appropriate comparator therapy					
Human insulin (bolus insulin)[7]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Human insulin (NPH insulin)[7]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Insulin detemir	3,000 U.	€ 144.80	€ 1.77	€ 7.41	€ 135.62
Insulin glargine	3,000 U.	€ 123.75	€ 1.77	€ 6.24	€ 115.74
Insulin aspart	3,000 U.	€ 123.99	€ 1.77	€ 6.26	€ 115.96
Insulin glulisine	3,000 U.	€ 124.01	€ 1.77	€ 6.26	€ 115.98
Insulin lispro	3,000 U.	€ 107.04	€ 1.77	€ 5.32	€ 99.95
Abbreviations: E. = units; I.U. = International Units; FCT = film-coated tablets					

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

[7] Fixed amount

of the cheapest pack in each case and shown on the basis of the pharmacy retail price level.

To detect possible diabetic ketoacidosis prior to and during treatment with dapagliflozin, ketone body measurements must be performed in the blood. Because the frequency of this measurement varies from patient to patient, the number of test strips to be used cannot be quantified more precisely. The measurement can be carried out both in the blood and in the urine. However, according to the product information, the measurement of the ketone body levels in the blood is preferable to measurement in the urine.

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/package[8]	Number	Consumption/year
Medicinal product to be assessed				
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
Dapagliflozin	Ketone body test strips (urine)	€ 7.26	Patient-individual	Patient-individual
	Ketone body test strips (blood)	€ 19.19	Patient-individual	Patient-individual
Appropriate comparator therapy				
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
Insulin detemir (monotherapy)	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
Insulin detemir + human insulin (bolus insulin)	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
Insulin glargine (monotherapy)	Blood sugar test strips	€ 18.50	1–3 × daily	365–1,095
	Lancets	€ 4.10	1–3 × daily	365–1,095

[8] 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 October 2019.

	Disposable needles	€ 16.90	1 × daily	365
Insulin glargine + human insulin (bolus insulin)	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 × daily	1,460
Insulin aspart + NPH insulin	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
Insulin glulisine + NPH insulin	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
Insulin lispro + NPH insulin	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

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.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 23 June 2015.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 9 April 2019.

On 17 April 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 1, sentence 2 VerfO.

By letter dated 18 April 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 30 July 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 August 2019. The deadline for submitting written statements was 22 August 2019.

The oral hearing was held on 9 September 2019.

By letter dated 9 September 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 27 September 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 8 October 2019, and the proposed resolution was approved.

At its session on 17 October 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	23 June 2015	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	9 April 2019	Redefinition of the appropriate comparator therapy
Working group Section 35a	3 September 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	9 September 2019	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 September 2019 1 October 2019	Consultation on the dossier evaluation of the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal product	8 October 2019	Concluding discussion of the proposed resolution
Plenum	17 October 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 October 2019

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The chair

Prof Hecken