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 Empagliflozin/Linagliptin

of 22 November 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

The relevant date for the first placing on the market of the fixed dose combination empagliflozin/linagliptin in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 June 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 29 May 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 2 September 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 empagliflozin/linagliptin 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, and the statements submitted in the written statement and oral hearing procedure. 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 empagliflozin/linagliptin.

In 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 empagliflozin/linagliptin (Glyxambi®) in accordance with the product information

Glyxambi, fixed dose combination of empagliflozin and linagliptin, is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Glyxambi do not provide adequate glycaemic control
- when already being treated with the free combination of empagliflozin and linagliptin[2].

(See Sections 4.2, 4.4, 4.5, and 5.1 for available data on combinations studied)

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with type 2 diabetes mellitus, whose blood sugar cannot be adequately controlled by diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin, here metformin and/or sulfonylurea and empagliflozin or linagliptin[2])

Appropriate comparator therapy:

- Human insulin + metformin or
- Human insulin + empagliflozin[3] or
- Human insulin + liraglutide[3] 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

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

[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] Linagliptin as a monopreparation is currently not on the market in Germany.

[3] 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 drugs, anticoagulants, and/or lipid-reducers (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).

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. Metformin, sulphonureas, and insulin (human insulin, insulin analogues) are authorised for the mono- and the combination therapy. Marketing authorisations for mono- as well as for the combination therapy also exist for other antidiabetics, 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 drugs, 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),
- 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 drug); 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 hypoglycaemiants; 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 hypoglycaemiants; for all other patient groups, the additional benefit is not proven).

On 4. The present therapeutic indication for the fixed combination empagliflozin/linagliptin (Glyxambi®) comprises adult patients with type 2 diabetes mellitus whose blood sugar cannot be sufficiently lowered with metformin and/or a sulfonylurea and one of the single active ingredients contained in Glyxambi®. The patients for whom the fixed combination of empagliflozin/linagliptin is indicated have thus already received at least two hypoglycaemic active ingredients.

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

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 and insulin are to be regarded as appropriate therapies in the therapeutic indication.

In addition, the resolution on empagliflozin is based on data of the EMPA-REG-Outcome Study. Based on the EMPA-REG study, empagliflozin in combination with human insulin is designated as part of the appropriate comparator therapy for patients with manifest cardiovascular disease and further medication for the treatment of cardiovascular risk factors[7]. 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 the advantages of liraglutide in cardiovascular endpoints, the G-BA concluded that in the present therapeutic indication, liraglutide in addition to human insulin is useful for patients with type 2 diabetes mellitus with manifest cardiovascular disease and further medication for the treatment of cardiovascular risk factors[7]. 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.

Thus, the combinations of empagliflozin or liraglutide with human insulin for patients with manifest cardiovascular disease constitute further options of the appropriate comparator therapy.

There has previously been a lack of long-term safety data on the further authorised active ingredients or groups of active ingredients in the therapeutic indication; these

[4] 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.

[5] 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.

[6] 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.

[7] In particular anti-hypertensive drugs, anticoagulants, and/or lipid reducers.

are therefore not taken into account as appropriate comparator therapy in the current assessment procedure.

Consequently, the combination of metformin and human insulin or the combinations of empagliflozin or liraglutide, each with human insulin (these only for patients with manifest cardiovascular disease[3]) is intended as an appropriate comparator therapy for adult patients with type 2 diabetes mellitus whose blood glucose cannot be sufficiently lowered with metformin and/or a sulfonylurea and one of the active ingredients contained in Glyxambi®.

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[3], or with liraglutide[3]. If metformin, empagliflozin,[3] and liraglutide[3] 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.

For insulin analogues, according to the generally acknowledged level of medical knowledge, there is neither an advantage nor a disadvantage compared to 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 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 in patients with type 2 diabetes mellitus, patient-specific treatment of the respective comorbidities (e.g. hypertension, dyslipoproteinemia, and CHD), in particular by antihypertensives, anticoagulants, and/or lipid-lowering agents, is carried out in accordance with the state of medical knowledge, taking into account the special features of the type 2 diabetes mellitus.

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 empagliflozin/linagliptin is assessed as follows:

For adult patients with type 2 diabetes mellitus, whose blood sugar cannot be adequately controlled by diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin, here metformin and/or sulfonylurea and empagliflozin or linagliptin[2]), the additional benefit is not proven.

Justification:

The pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of empagliflozin/linagliptin compared with the appropriate comparator therapy.

Instead of submitting randomised controlled trials for a direct comparison with the appropriate comparator therapy, the pharmaceutical company describes in the dossier the placebo-controlled Phase III studies 1275.9 and 1275.10 for empagliflozin/linagliptin relevant for marketing authorisation as well as the respective cardiovascular outcome studies for the individual substances (CARMELINA and CAROLINA for linagliptin and EMPA-REG OUTCOME for empagliflozin). The pharmaceutical company states that these studies would provide supporting evidence to characterise the additional benefit of empagliflozin/linagliptin with respect to their efficacy and safety results. However, the studies mentioned are not relevant for assessing the additional benefit of empagliflozin/linagliptin. On one hand, in the pivotal studies 1275.9 and 1275.10 empagliflozin/linagliptin are not compared with the appropriate comparator therapy. On the other hand, in the CARMELINA, CAROLINA, and EMPA-REG OUTCOME cardiovascular outcome studies, only the individual substances linagliptin or empagliflozin are investigated. These further studies therefore do not provide relevant results for the present fixed dose combination of empagliflozin/linagliptin.

For indirect comparisons, the pharmaceutical company first identifies the pivotal studies 1275.9 and 1275.10 with the fixed dose combination empagliflozin/linagliptin and metformin to be evaluated in comparison with linagliptin and metformin or empagliflozin and metformin. Because no studies with the bridge comparators linagliptin and metformin or empagliflozin and metformin were found in comparison with the appropriate comparator therapy human insulin and metformin, the pharmaceutical company refrained from carrying out an indirect comparison.

Studies 1275.9 and 1275.10 are therefore not used for the benefit assessment because they do not contain suitable data that allow a direct comparison of empagliflozin/linagliptin with the appropriate comparator therapy. The cardiovascular outcome studies of the individual substances also do not provide suitable data for the benefit assessment of the present fixed dose combination of empagliflozin/linagliptin because the fixed dose combination was not investigated.

For an indirect comparison, no relevant studies with a bridge comparator that would have been suitable for assessing the additional benefit compared with the appropriate comparator therapy were identified.

Overall, there are no adequate studies or an indirect comparison for the benefit assessment of empagliflozin/linagliptin.

2.1.4 Summary of the assessment

In the context of the benefit assessment, the pharmaceutical company presents the results of the existing pivotal studies of empagliflozin/linagliptin and the cardiovascular outcome studies of the individual substances empagliflozin and linagliptin because there are none directly comparative studies for empagliflozin/linagliptin compared with the appropriate comparator therapy as well as studies that would allow an indirect comparison. The presented studies by the pharmaceutical company are not suitable for the benefit assessment of empagliflozin/linagliptin because they do not allow a comparison between the fixed dose combination empagliflozin/Linagliptin to be evaluated and the appropriate comparator therapy determined by the G-BA. Overall, there are no adequate studies for the benefit assessment of empagliflozin/linagliptin. An additional benefit is therefore not proven.

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 of the corresponding therapy situations indicated for antidiabetic drugs in resolutions already adopted in accordance with Section 35a SGB V, possibly taking into account a range. This takes into account the uncertainties concerning the restricted epidemiological data basis on type 2 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 Glyxambi® (active ingredient: empagliflozin/linagliptin) at the following publicly accessible link (last access: 15 October 2019):
https://www.ema.europa.eu/documents/product-information/glyxambi-epar-product-information_de.pdf

The use of DPP4 inhibitors (e.g. linagliptin) was associated with a risk of developing acute pancreatitis. Patients should be informed about characteristic symptoms of acute pancreatitis, and the therapy should be changed if necessary.

Overall, the current data basis with regard to pancreatic carcinomas is not clear[8,9]. In view of the lack of a conclusive assessment of the risk of pancreatic carcinoma or pancreatic damage in this substance class, increased monitoring of patients for pancreatic diseases is recommended. In suspected cases, DPP4 inhibitor-based therapy should be dispensed with.

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: 15 October 2019).

Concerning the usage and consumption, the average annual consumption was calculated by indicating the number of tablets (TAB), single doses (SD), units (U), or I.U.[10]. 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.

For empagliflozin/linagliptin a once daily application is intended. The initial dose is 10 mg empagliflozin and 5 mg linagliptin. The recommended daily dose is 25 mg empagliflozin and 5 mg linagliptin.

[8] https://cordis.europa.eu/result/rcn/183717_de.html [Accessed: 7 October 2019]
[9] https://www.akdae.de/Arzneimitteltherapie/AVP/Artikel/201703/112.pdf [Accessed: 7 October 2019]
[10] I.U. = international unit.

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.

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 empagliflozin, an initial dosage of 10 mg once daily as combination therapy with other hypoglycaemiants 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.

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[11], 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[12].

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				
Empagliflozin/linagliptin	continuous, 1 × daily	365	1	365
Appropriate comparator therapy				
Human insulin (NPH insulin)	continuous, 1–2 × daily	365	1	365

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

[12] 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].

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/ patient/year
Conventional insulin therapy (premixed insulin)	continuous, 1–2 × daily	365	1	365
Combination partner for human insulin				
Empagliflozin	continuous, 1 × daily	365	1	365
Liraglutide	continuous, 1 × daily	365	1	365
Metformin	continuous, 2–3 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage	Dose/ patient/ treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption by potency
Medicinal product to be assessed					
Empagliflozin/ linagliptin	10 mg/5 mg or 25 mg/5 mg	10 mg/5 mg or 25 mg/5 mg	1 × 10 mg/5 mg or 1 × 25 mg/5 mg	365	365 × 10 mg/5 mg - 365 × 25 mg/5 mg
Appropriate comparator therapy					
Human insulin (NPH insulin)[13]	0.5–1 I.U. per kg/BW	38.50 to 77 I.U.	1 × 38.5 I.U. –1 × 77 I.U.	365	14,052.5 I.U. – 28,105 I.U.
Conventional insulin therapy (premixed insulin)[13]	0.5–1 I.U. per kg/BW	38.50 to 77 I.U.	1 × 38.5 I.U. –1 × 77 I.U.	365	14,052.5 I.U. – 28,105 I.U.
Combination partner for human insulin					
Empagliflozin	10 mg or 25 mg	10 mg or 25 mg	1 × 10 mg or 1 × 25 mg	365	365 × 10 mg - 365 × 25 mg
Liraglutide	1.2 mg or 1.8 mg [14]	1.2 mg or 1.8 mg	1 × 1.2 mg or 1 × 1.8 mg	365	365 × 1.2 mg or 365 × 1.8 mg
Metformin	500 mg – 1,000 mg	1,000 mg – 3,000 mg	1 × 1,000 mg –3 × 1,000 mg	365	365 × 1,000 mg – 1095 × 1,000 mg

Costs:

[13] Average insulin requirement: 0.5–1.0 I.U./kg body weight /day; reference: 77 kg body weight (BW) ("Microcensus 2017"[12]).

[14] 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.

Costs of the medicinal product:

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

To calculate the costs of the medicinal products, 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.

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 wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Empagliflozin/linagliptin 10 mg/5 mg and 25 mg/5 mg	100FTA	€ 339.71	€ 1.77	€ 18.20	€ 319.74
Appropriate comparator therapy					
Human insulin 100 I.U. (NPH)[15]	3000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Conventional insulin therapy 100 I.U. (Premixed insulin)[15]	3000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Combination partner for human insulin					
Empagliflozin (10 mg or 25 mg)	100 FCT	€ 192.34	€ 1.77	€ 10.04	€ 180.53
Liraglutide	100–150 SD	€ 570.64	€ 1.77	€ 30.99	€ 537.88
Metformin[15] (1000 mg)	180 FCT	€ 18.78	€ 1.77	€ 0.62	€ 16.39
Abbreviations: SD = single doses; I.E. = International Units; FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 October 2019

<u>Costs for additionally required SHI services:</u>

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.

[15] Fixed amount

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

The use of liraglutide results in additional costs in the form of disposable needles.

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/package[16]	Number	Consumption/year
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
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.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 7 June 2016.

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 21 November 2017.

On 29 May 2019, the pharmaceutical company submitted a dossier for the benefit assessment of empagliflozin/linagliptin to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

[16] 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: 15 October 2018.

By letter dated 29 May 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 fixed dose combination empagliflozin/linagliptin.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 August 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 September 2019. The deadline for submitting written statements was 23 September 2019.

The oral hearing was held on 7 October 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 12 November 2019, and the proposed resolution was approved.

At its session on 22 November 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	21 November 2017	Determination of the appropriate comparator therapy
Working group Section 35a	1 October 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 October 2019	Conduct of the oral hearing
Working group Section 35a	15 October 2019 22 October 2019	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	29 October 2019	Concluding discussion of the proposed resolution
Plenum	22 November 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 22 November 2019

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

Prof Hecken