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 Insulin Glargine/Lixisenatide (New Therapeutic Indication: Type 2 Diabetes Mellitus, Combination with Metformin and with SGLT-2 Inhibitors)

of 15 October 2020

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 proof and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides 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 combination insulin glargine/lixisenatide (Suliqua®) was listed for the first time on 1 March 2018 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 9 March 2020, insulin glargine/lixisenatide 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 3 April 2020, the pharmaceutical company submitted the final 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 VerfO to the G-BA in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication.

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 15 July 2020, 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 insulin glargine/lixisenatide 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 assessed 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 insulin glargine/lixisenatide.

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 insulin glargine/lixisenatide (Suliqua ®) in accordance with the product information

Suliqua is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to metformin with or without SGLT-2 inhibitors. (For study results with respect to effect on glycaemic control, and the populations studied, see section 4.4 and 5.1).

The present resolution refers to the new combination therapy consisting of insulin glargine/lixisenatide + metformin + SGLT-2 inhibitors.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with type 2 diabetes mellitus who are not adequately controlled by treatment with at least two hypoglycaemic agents (except insulin)

Appropriate comparator therapy:

- Human insulin + metformin or
- Human insulin + empagliflozin or
- Human insulin + liraglutide 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

  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-lowering agents[2]

b) Adult patients with type 2 diabetes mellitus who are not adequately controlled by treatment with insulin (with or without another hypoglycaemic agents)

Appropriate comparator therapy:

[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] 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

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

  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-lowering agents[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. 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 applications 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, sulphonureas, 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-diabetics, 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 applications 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),
- Lixisenatide (Resolution of 5 September 2013: An additional benefit is not proven; for the combination with oral anti-diabetics, 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),
- 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),
- 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 glargine/lixisenatide (Resolution of 16 August 2018: An additional benefit is not proven).
- Ertugliflozin/sitagliptin (Resolution 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).

- Empagliflozin/linagliptin (Resolution of 22 November 2019: An additional benefit is not proven).
- Dapagliflozin (Resolution of 19 December 2019: Hint for a minor additional benefit in combination therapy of dapagliflozin with one or more hypoglycaemic agents and only for patients at high cardiovascular risk receiving further medication for the treatment of cardiovascular risk factors; for all other patient groups, the additional benefit is not proven).
- Dapagliflozin/metformin (Resolution of 19 December 2019: Hint for a minor additional benefit only for patients at high cardiovascular risk receiving further medication for the treatment of cardiovascular risk factors; for all other patient groups, the additional benefit is not proven).
- Dulaglutide (Resolution of 16 July 2020: hint for a minor additional benefit only for the combination with insulin (with or without an oral antidiabetic agent), in each case in patients with or without renal insufficiency; for all other patient groups, the additional benefit is not proven),

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in this indication.

In the present therapeutic indication, the fixed combination insulin glargine/lixisenatide is approved only in combination with metformin. The patients treated with the fixed combination are thus treated with a combination therapy of 3 or 4 hypoglycaemicagents , including insulin.

It must therefore be assumed that insulin therapy is indicated for patients who are eligible for insulin glargine/lixisenatide in combination with metformin (with or without SGLT-2 inhibitors). Thus, only the therapy situations in which an insulin therapy is indicated are considered.

In addition, it is assumed that a pharmacotherapy is started only after failure of a single basic therapy (e.g. non-medicinal measures such as diet and movement) and is always carried out in combination with this.

Metformin is a first-choice oral anti-diabetic agent with proven reduction of overall mortality and heart attack risk[3,4]. For human insulin, a reduction of diabetes-related microvascular complications is proven[5].

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.

Consequently, after failure of two oral anti-diabetics, the combination of metformin and human insulin represents a standard therapy in the therapeutic indication regularly used in clinical practice and was therefore determined as an appropriate comparator therapy in patient group a).

[3] 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.
[4] 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.
[5] 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

In addition, the resolution on empagliflozin is based on positive study results from the EMPA-REG Outcome study on cardiovascular endpoints in patients with type 2 diabetes mellitus and manifest cardiovascular disease. Based on the EMPA-REG Outcome study, empagliflozin in combination with human insulin for patients with type 2 diabetes mellitus with manifest cardiovascular disease and further medication for the treatment of cardiovascular risk factors was designates as part of the appropriate comparator therapy. 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 proof of a cardiac disorder, ischaemic or haemorrhagic stroke, or peripheral arterial occlusive disease with clinically relevant ischaemia[6].

In addition, for liraglutide, the Rapid Report of the IQWiG on the cardiovascular long-term study LEADER is available. Based on the positive study results in cardiovascular endpoints, the G-BA concluded that liraglutide in addition to at least one other hypoglycaemic agent (including insulin) for patients with type 2 diabetes mellitus with manifest cardiovascular disease and further medication for the treatment of cardiovascular risk factors[7] 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)[8]. Furthermore, in the LEADER study, for patients with renal insufficiency with an eGFR < 60 ml/min/1.73 m^2, there were advantages for overall mortality, stroke, and the combined endpoint MACE.

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

For the other active ingredients or groups of active ingredients approved in the therapeutic indication, for some of which cardiovascular endpoint studies are available, either no positive effects on patient-relevant endpoints have been proven or the effects are only minor. These active ingredients are therefore not considered as appropriate comparator therapies.

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

On patient group “a)” *(Adult patients with type 2 diabetes mellitus who are not adequately controlled by treatment with at least two hypoglycaemic agents (except insulin))*: 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 therapy situation, insulin therapy may be indicated in combination with metformin, empagliflozin, or liraglutide. If metformin, empagliflozin, and liraglutide 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.

According to the generally recognised state of medical knowledge for patients of patient group “b)” (*Adult patients with type 2 diabetes mellitus who are not adequately controlled*

[6] Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–28. DOI: 10.1056/NEJMoa1504720.
[7] In particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents.
[8] Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375: 311–322. DOI: 10.1056/NEJMoa1603827.

by treatment with insulin (with or without another hypoglycaemic agents), an optimisation of the human insulin regime is recommended. This can be achieved through various forms of insulin therapy (e.g. conventional insulin therapy (CT) or intensified conventional insulin therapy (ICT). In the course of an ICT, the administration of an additional hypoglycaemiant is not regularly considered to be indicated.

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 drugs, 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 glargine 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 insulin glargine/lixisenatide is assessed as follows:

a) Adult patients with type 2 diabetes mellitus who are not adequately controlled by treatment with at least two hypoglycaemic agents (except insulin)

   An additional benefit is not proven.

b) Adult patients with type 2 diabetes mellitus who are not adequately controlled by treatment with insulin (with or without another hypoglycaemic agents)

   An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of insulin glargine/lixisenatide as an adjunct to diet and exercise for the treatment of adult patients with insufficiently controlled type 2 diabetes mellitus according to the new therapeutic indication in addition to metformin and an SGLT-2 inhibitor, no data were presented compared with the appropriate comparator therapy determined in patient groups a) and b). The additional benefit is thus not proven.

<u>Extent and probability of the additional benefit</u>

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient combination insulin glargine/lixisenatide.

Therapeutic indication (according to the marketing authorisation of 9 March 2020):

“Suliqua is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to metformin with or without SGLT-2 inhibitors”.

The assessment relates exclusively to the new combination of insulin glargine/lixisenatide with metformin and an SGLT-2 inhibitor.

In the therapeutic indication to be considered, 2 patient groups were distinguished.

a) Adult patients with type 2 diabetes mellitus who are not adequately controlled by treatment with at least two hypoglycaemic agents (except insulin)

and

b) Adult patients with type 2 diabetes mellitus who are not adequately controlled by treatment with insulin (with or without another hypoglycaemic agents).

Patient group a)

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

- Human insulin + metformin or
- Human insulin + empagliflozin or
- Human insulin + liraglutide
- 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

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-lowering agents.

No data compared with the appropriate comparator therapy were provided. The additional benefit is thus not proven.

Patient group b)

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 or liraglutide)

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-lowering agents.

No data compared with the appropriate comparator therapy were provided. The additional benefit is thus not proven.

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

This information on the number of patients refers to 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.

In accordance with the marketing authorisation, insulin glargine/lixisenatide may be prescribed only in combination with metformin or with metformin and SGLT-2 inhibitors. Because metformin is primarily prescribed if tolerated, it can be assumed that patients without metformin prescription have an intolerance or contraindications and are therefore not eligible for therapy with insulin glargine/lixisenatide. Even though the change in the therapeutic indication means that it is no longer mandatory to prescribe previous therapy with metformin, it is also assumed that patients receiving insulin glargine/lixisenatide had usually undergone previous therapy with metformin. Against this background, in the present case, the updated patient numbers from the dapagliflozin/metformin resolution[9] based on the IQWiG working paper[10] are used in accordance with the corresponding patient groups b) and c). Only those patients who receive or maintain therapy with metformin are considered. The present patient numbers differ from the patient numbers in the initial resolution on insulin glargine/lixisenatide of 16 August 2018 in that the latter are based on different, non-updated data.

However, the G-BA points out that the data on patient numbers are subject to uncertainty. In accordance with the product information, insulin glargine/lixisenatide is used for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control. However, it is assumed that not all patients with inadequately controlled type 2 diabetes mellitus who are treated in clinical practice with the fixed combination of insulin glargine/lixisenatide actually receive a fourfold combination of insulin glargine/lixisenatide with metformin and SGLT-2 inhibitors. Against this background, it cannot be ruled out that the patient numbers used for the calculation are overestimated.

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 Suliqua® (fixed active ingredient combination: insulin glargine/lixisenatide) at the following publicly accessible link (last access: 24 August 2020):

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

The use of GLP-1 receptor agonists (e.g. lixisenatide) 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.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material. The training material should inform health care professionals and patients about the risk of medication errors, including confusion about the different potencies of the medicinal product.

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 September 2020).

[9] Resolution of 19 December 2019 (patient group b) Adult patients with type 2 diabetes mellitus in whom diet and movement and treatment with at least two hypoglycaemiants (including metformin, apart from insulin) do not sufficiently control the blood sugar and c) Adult patients with type 2 diabetes mellitus in whom diet and movement and treatment with insulin (with one other hypoglycaemic agent, here metformin) do not sufficiently control the blood sugar
https://www.g-ba.de/downloads/39-261-4089/2019-12-19_AM-RL-XII_Dapagliflozin-Metformin_D-462_BAnz.pdf
[Access 10 September 2020]

[10] https://www.iqwig.de/download/GA16-03_Routinedaten-bei-Diabetes-mellitus-Typ-2_Arbeitspapier_V1-1.pdf

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.[11]. 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 insulin glargine/lixisenatide, a once daily application is intended. The maximum daily dose is 60 units of insulin glargine and 20 µg of lixisenatide. The potency 10 units of insulin glargine and 5 µg lixisenatide is currently not on the market. The consumption of 30 units of insulin glargine and 10 µg of lixisenatide was therefore used as the lower range.

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 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.

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 mixed insulin) is represented as "1–2 × daily" even if the application frequency can deviate in some patients. According to the product information[12] , 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[13].

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 kg are not taken into account for the cost calculation.

[11] I.U. = international unit.
[12] Product information on Insuman® Basal, last revised: April 2018.
[13] 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

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) and b)				
Insulin glargine/lixisenatide	continuously, 1 × daily	365	365	
+ metformin	continuously, 2–3 × daily	365	1	365
+ empagliflozin	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
Human insulin (NPH insulin)	continuously, 1–2 × daily	365	1	365
+ metformin or	continuously, 2–3 × daily	365	1	365
+ empagliflozin or	continuously, 1 × daily	365	1	365
+ liraglutide or	continuously, 1 × daily	365	1	365
Conventional insulin therapy				
Mixed insulin	continuously, 1–2 × daily	365	1	365
Patient population b)				
Intensified conventional insulin therapy				
Human insulin (bolus insulin) +	continuously, 3 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Human insulin (NPH insulin)	continuously, 1–2 × daily	365	1	365
Conventional insulin therapy				
Mixed 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

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Patient population a) and b)					
Insulin glargine/lixisenatide	30 U/10 µg	30 U/10 µg	1 × 30 U/10 µg	365	365 × 30 U/10 µg –
Insulin glargine/lixisenatide	60 U/20 µg	60 U/20 µg	1 × 60 U/20 µg	365	365 × 60 U/20 µg
+ 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
+ empagliflozin	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
	25 mg	25 mg	1 × 25 mg		365 × 25 mg

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Patient population a)					
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.		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[14]	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
Conventional insulin therapy					
Mixed insulin	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.		28,105 I.U.
Patient population b)					
Intensified conventional insulin therapy[15]					
Human insulin (NPH insulin) +	0.2 –	15.4 –	1 × 15.4 -	365	5,621 I.U.–
	0.6 I.U. per kg/BW	46.2 I.U.	1 × 46.2 I.U.		16,863 I.U.
Human insulin (bolus insulin)	0.2 –	15.4 –	1 × 15.4 -	365	5,621 I.U.–
	0.6 I.U. per kg/BW	46.2 I.U.	1 × 46.2 I.U.		16,863 I.U.

[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.
[15] 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	Average annual consumption by potency
Conventional insulin therapy					
Mixed insulin	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.		28,105 I.U.
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[14]	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:

The calculation of the treatment costs for the active ingredients metformin, human insulin and mixed 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 sales 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 mixed insulin (i.e. a human insulin preparation in a certain premixing ratio of 30% normal insulin to 70% basal insulin).

Costs of the medicinal product:

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
Patient population a) and b)					
Insulin glargine/lixisenatide 100 U/ml + 33 µg/ml	10 × 3 ml SFI	€ 187.62	€ 1.77	€ 10.05	€ 175.80
Insulin glargine/lixisenatide 100 U/ml + 50 µg/ml	Currently not on the market				
+ metformin[16] 1,000 mg	180 FCT	€ 18.36	€ 1.77	€ 0.62	€ 15.97
+ empagliflozin 10 mg	100 FCT	€ 187.55	€ 1.77	€ 10.04	€ 175.74
+ empagliflozin 25 mg	100 FCT	€ 187.55	€ 1.77	€ 10.04	€ 175.74
Appropriate comparator therapy					
Empagliflozin 10 mg	100 FCT	€ 187.55	€ 1.77	€ 10.04	€ 175.74
Empagliflozin 25 mg	100 FCT	€ 187.55	€ 1.77	€ 10.04	€ 175.74
Human insulin (bolus insulin)[16]	3,000 I.U.	€ 87.44	€ 1.77	€ 6.22	€ 79.45
Human insulin (NPH insulin) [16]	3,000 I.U.	€ 87.44	€ 1.77	€ 6.22	€ 79.45
Metformin[16] 1,000 mg	180 FCT	€ 18.36	€ 1.77	€ 0.62	€ 15.97
Mixed insulin[16]	3,000 I.U.	€ 87.44	€ 1.77	€ 6.22	€ 79.45
Liraglutide 18 mg	100 – 150 SD	€ 556.31	€ 1.77	€ 30.99	€ 523.55
Abbreviations: SD = single doses; FCT = film-coated tablets, I.U. = international units; SFI = solution for injection; TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 September 2020

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

[16] Fixed reimbursement rate

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/package[17]	Number	Consumption/year
Medicinal product to be assessed				
Insulin glargine/lixisenatide	Blood sugar test strips	€ 15.95	1–3 × daily	365–1,095
	Lancets	€ 4.10	1–3 × daily	365–1,095
	Disposable needles	€ 16.90	1 × daily	365
Appropriate comparator therapy				
Human insulin (NPH insulin) as well as Conventional insulin therapy (mixed insulin)	Blood sugar test strips	€ 15.95	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	€ 15.95	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.

4. Process sequence

At its session on 7 April 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 3 April 2020, the pharmaceutical company submitted a dossier for the benefit assessment of insulin glargine/lixisenatide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

[17] 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 September 2020.

By letter dated 14 April 2020 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 insulin glargine/lixisenatide.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 July 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 July 2020. The deadline for submitting written statements was 5 August 2020.

The oral hearing was held on 24 August 2020.

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 6 October 2020, and the proposed resolution was approved.

At its session on 15 October 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	7 April 2020	Determination of the appropriate comparator therapy
Working group Section 35a	19 August 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	24 August 2020	Conduct of the oral hearing
Working group Section 35a	2 September 2020 16 September 2020 30 September 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	6 October 2020	Concluding discussion of the draft resolution
Plenum	15 October 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 15 October 2020

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

Prof. Hecken