Resolution

Gemeinsamer Bundesausschuss

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

At its session on 15 October 2020 the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive, (AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of insulin glargine/lixisenatide in accordance with the resolution of 16 August 2018, last amended on 4 July 2019:

Insulin glargine/lixisenatide

Resolution of: 15 October 2020
Entry into force on: 15 October 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New 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. (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.

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

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[1]

Extent and probability of the additional benefit of insulin glargine/lixisenatide + metformin + SGLT-2 inhibitors compared with the appropriate comparator therapy:

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)

Appropriate comparator therapy:

- 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[1]

[1] 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

Extent and probability of the additional benefit of insulin glargine/lixisenatide + metformin + SGLT-2 inhibitors compared with the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:

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

There are no relevant data in comparison to the appropriate comparator therapy.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data relevant for the benefit assessment were submitted.
Morbidity	∅	No data relevant for the benefit assessment were submitted.
Health-related quality of life	∅	No data relevant for the benefit assessment were submitted.
Side effects	∅	No data relevant for the benefit assessment were submitted.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

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

There are no relevant data in comparison to the appropriate comparator therapy.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/	Summary

	Risk of bias	
Mortality	∅	No data relevant for the benefit assessment were submitted.
Morbidity	∅	No data relevant for the benefit assessment were submitted.
Health-related quality of life	∅	No data relevant for the benefit assessment were submitted.
Side effects	∅	No data relevant for the benefit assessment were submitted.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 261,000 patients

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

approx. 271,000 patients

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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Insulin glargine/lixisenatide	€ 641.67 – 1,283.34
Metformin	€ 32.38 – 97.15
Empagliflozin[2]	€ 641.45
	Total:
Insulin glargine/lixisenatide + metformin + empagliflozin	€ 1,315.50 – 2,021.94
Appropriate comparator therapy:	
Metformin	€ 32.38 – 97.15
Empagliflozin	€ 641.45
Liraglutide	€ 1,273.97 – 1,910.96
Human insulin (NPH insulin)	€ 372.16 – 744.31
	Total:
Human insulin (NPH-insulin) + metformin	€ 404.54 – 841.46
Human insulin (NPH insulin) + empagliflozin	€ 1,013.61 – 1,385.77
Human insulin (NPH insulin) + 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	€ 1,646.13 – 2,655.27
Possibly therapy only with human insulin if, in accordance with the product information, metformin and empagliflozin and liraglutide are incompatible or contraindicated or are not sufficiently effective because of an advanced type 2 diabetes mellitus	
Conventional insulin therapy (mixed insulin)	€ 372.16 – 744.31

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2020

[2] Empagliflozin is listed as an example for the combination with an SGLT-2 inhibitor

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/year
Medicinal product to be assessed		
Insulin glargine/lixisenatide	Blood glucose test strips Lancets Disposable needles	€ 116.44 – 349.31 € 7.48 – 22.45 € 61.69
Appropriate comparator therapy		
Human insulin (NPH insulin) as well as conventional insulin therapy (mixed insulin)	Blood glucose test strips Lancets Disposable needles	€ 116.44 – 349.31 € 7.48 – 22.45 € 61.69 – 123.37
Liraglutide	Disposable needles	€ 61.69

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Insulin glargine/lixisenatide	€ 641.67 – 1,283.34
Metformin	€ 32.38 – 97.15
Empagliflozin[3]	€ 641.45
	Total:
Insulin glargine/lixisenatide + metformin + empagliflozin	€ 1,315.50 – 2,021.94
Appropriate comparator therapy:	
Metformin	€ 32.38 – 97.15
Empagliflozin	€ 641.45
Liraglutide	€ 1,273.97 – 1,910.96
Conventional insulin therapy (mixed insulin)	€ 372.16 – 744.31
Conventional insulin therapy (mixed insulin) possibly + metformin *or* empagliflozin *or* liraglutide Conventional insulin therapy (mixed insulin) + metformin	Total: € 404.54 – 841.46 € 1,013.61 – 1,385.77

[3] Empagliflozin is listed as an example for the combination with an SGLT-2 inhibitor

Designation of the therapy	Annual treatment costs/patient
Conventional insulin therapy (mixed insulin) + empagliflozin Conventional insulin therapy (mixed insulin) + 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	€ 1,646.13 – 2,655.27
Intensified conventional insulin therapy	
Human insulin (NPH insulin)	€ 148.86 – 446.59
Human insulin (bolus insulin)	€ 148.86 – 446.59
Total:	Total:
	€ 372.16 – 744.31

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2020

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/year
Medicinal product to be assessed		
Insulin glargine/lixisenatide	Blood glucose test strips Lancets Disposable needles	€ 116.44 – 349.31 € 7.48 – 22.45 € 61.69
Appropriate comparator therapy		
Conventional insulin therapy (mixed insulin)	Blood glucose test strips Lancets Disposable needles	€ 116.44 – 349.31 € 7.48 – 22.45 € 61.69 – 123.37
Intensified conventional insulin therapy	Blood glucose test strips Lancets Disposable needles	€ 465.74 – 698.61 € 29.93 – 44.90 € 246.74 – 308.43
Liraglutide	Disposable needles	€ 61.69

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 15 October 2020.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 15 October 2020

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

Prof. Hecken