Justification

Gemeinsamer Bundesausschuss

of 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 ingredient according to Section 35a SGB V (reassessment based on new scientific evidence) Semaglutide (Diabetes mellitus type 2)

of 15 April 2021

Contents

Courtesy translation – only the German version is legally binding.

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 submission 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:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th 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 decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient semaglutide was first marketed on 1 February 2018. In its session on 2 May 2019, the G-BA decided on the benefit assessment of semaglutide in accordance with Section 35a SGB V. By resolution of 16 April 2020, the G-BA, at the request of its members, initiated a new benefit assessment pursuant to Section 35a (1) SGB V in conjunction with Section 3 (1) No. 4 AM-NutzenV and Chapter 5 Section 13 of the Rules of Procedure (VerfO) for the active ingredient semaglutide. The new benefit assessment was prompted by new scientific findings from the completed PIONEER 6 study.

The relevant date for submission of the combination of active ingredient semaglutide in accordance with Chapter 5, Section 8, paragraph 1, number 6 of the Rules of Procedure of the G-BA (VerfO) is 1 November 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 41 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 October 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 February 2021 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

Courtesy translation – only the German version is legally binding.

The G-BA came to a resolution on whether an additional benefit of semaglutide 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 semaglutide.

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

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

2.1.1 Authorised therapeutic indication of semaglutide (Rybelsus/Ozempic) according to the product information

Therapeutic indication (according to the marketing authorisation of 8 February 2018 and 3 April 2020):

Ozempic is indicated for the treatment of adults with insufficiently controlled diabetes mellitus type 2 as an addition to diet and exercise

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

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and populations studied, see sections 4.4, 4.5, and 5.1.

Rybelsus s is indicated for the treatment of adults with insufficiently controlled diabetes mellitus type 2 to improve glycaemic control as an addition to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in combination with other medicinal products for treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and populations studied, see sections 4.4, 4.5, and 5.1.

Therapeutic indication of the resolution (resolution from the 15/04/2021):

see therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with diabetes mellitus type 2 for whom diet and exercise alone do not adequately control blood glucose and for whom the use of metformin is not appropriate due to intolerance

[1] General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Courtesy translation – only the German version is legally binding.

a1) in patients without established cardiovascular disease[2]

Appropriate comparator therapy:

- Sulfonylureas (glibenclamide or glimepiride)

a2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

Appropriate comparator therapy:

- Sulfonylureas (glibenclamide or glimepiride)

b) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with one hypoglycaemic agent (other than insulin) do not adequately control blood glucose

b1) in patients without established cardiovascular disease[2]

Appropriate comparator therapy:

- Metformin + sulfonylureas (glibenclamide or glimepiride) or
- Metformin + empagliflozin *or*
- Human insulin, if metformin is intolerant or contraindicated according to the product information

b2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

Appropriate comparator therapy:

- Metformin + sulfonylureas (glibenclamide or glimepiride) or
- Metformin + empagliflozin *or*
- Metformin + liraglutide[4] *or*
- Human insulin, if metformin is intolerant or contraindicated according to the product information

c) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with at least two hypoglycaemic agents (other than insulin) do not adequately control blood glucose

---

[2] established cardiovascular disease can be determined in the present case on the basis of the SUSTAIN 6 and PIONEER 6 studies (see study protocols, Marso et. al. Semaglutide and Cardiovascular Outcomes in Patients with Diabetes Type 2. N Engl J Med 2016; 375:1834-1844. DOI: 10.1056/NEJMoa1607141 or Husain et al. Oral semaglutide and cardiovascular outcomes in patients with diabetes type 2. N Engl J Med 2019; 381(9): 841-851. https://dx.doi.org/10.1056/NEJMoa1901118.) defined and summarized here approximately as ≥ 50 years of age with at least one cardiovascular disorder (previous myocardial infarction; Stroke or transient ischemic attack; revascularisation; > 50% stenosis; previous symptomatic coronary artery disease or unstable angina; asymptomatic cardiac ischemia, chronic heart failure (NYHA class II-III) or chronic renal failure) or ≥ 60 years of age with at least one risk factor for cardiovascular disease (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or Ankle Brachial Index < 0.9).

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

[4] Empagliflozin or liraglutide only for patients with established cardiovascular disease who are receiving additional medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants and/or lipid-lowering agents (for 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).

Courtesy translation – only the German version is legally binding.

c1) in patients without established cardiovascular disease[2]

Appropriate comparator therapy:

- Human insulin + metformin *or*
- only human insulin if metformin is intolerable or contraindicated according to the product information or is not sufficiently effective due to advanced diabetes mellitus type 2

c2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

Appropriate comparator therapy:

- Human insulin + metformin *or*
- Human insulin + empagliflozin[4] *or*
- Human insulin + liraglutide[4] *or*
- Human insulin, if the specific combination partners are intolerable or contraindicated according to the product information or are not sufficiently effective due to advanced diabetes mellitus type 2

d) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose

d1) in patients without established cardiovascular disease[2]

Appropriate comparator therapy:

- The optimisation of the human insulin regime (+ metformin, if necessary)

d2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

Appropriate comparator therapy:

- The optimisation of the human insulin regime (if necessary + metformin *or* empagliflozin[4] *or* liraglutide[4])

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

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

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

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

Courtesy translation – only the German version is legally binding.

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, sulfonylureas and insulin (human insulin, insulin analogues) are approved for monotherapy and combination therapy. Marketing authorisation for both monotherapy and combination therapy also exist for other anti-diabetic agents, including alpha-glucosidase inhibitors, dipeptidyl-peptidase-4 inhibitors (gliptides), glinides, SGLT-2 inhibitors (gliflozins), and incretin mimetics.

on 2. A non-medicinal treatment cannot be considered 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 considered not proven, for the combination with metformin the additional benefit is not proven; resolution of 16 May 2013 (new therapeutic indication): An additional benefit is not proven).
- Lixisenatide (Resolution of 5 September 2013: An additional benefit is not proven, for the combination with oral anti-diabetics the additional benefit is not 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 considered not proven); Resolution of 20 August 2015 (new therapeutic indication): An additional benefit is not proven; Resolution of 16 May 2019 (reassessment due to new scientific evidence related exclusively to the treatment of adult patients with diabetes mellitus type 2): 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 of a minor additional benefit for the combination with metformin, for other therapy 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: Hint for substantial additional benefit for patients with established cardiovascular disease in combination with further medication to treat cardiovascular risk factors for the combination with one

Courtesy translation – only the German version is legally binding.

or more hypoglycaemic agents; evidence of minor additional benefit for patients without established cardiovascular disease for the combination with metformin; for all other patient groups the additional benefit is not proven),

- Empagliflozin/Metformin (1 September 2016 Resolution: 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 metfomin; for all other patient groups, the additional benefit is not proven; Resolution of 22 March 2019 (renewed benefit assessment after date of expiry related exclusively to the two-drug 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, Resolution of 15 October 2020: 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: Hint for a minor additional benefit for patients with established cardiovascular disease in combination with further medication for the treatment of cardiovascular risk factors for the combination with one or more 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 the combination therapy of dapagliflozin with one or more hypoglycaemic agents and only for patients with high cardiovascular risk who receive 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 with high cardiovascular risk who receive 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 for adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose; for all other patient groups, the additional benefit is not proven).

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

Courtesy translation – only the German version is legally binding.

Metformin is the oral anti-diabetic of first choice with proven reduction in all-cause mortality and risk of myocardial infarction[5,6]. Human insulin has been shown to reduce diabetes-related microvascular complications[7].

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

For empagliflozin in the two-drug combination with metformin, positive study results are available from study 1245.28 and the EMPA-REG-Outcome study regarding cardiovascular endpoints of empagliflozin for patients with diabetes mellitus type 2 with established cardiovascular disease only. For the two-drug combination empagliflozin with metformin, there was a hint for a minor additional benefit compared to the appropriate comparator therapy metformin in combination with sulfonylureas (glimepiride) for all patients with diabetes mellitus type 2 and was therefore designated as part of the appropriate comparator therapy in this patient group.
In addition, based on the EMPA-REG-Outcome study, there was a hint for a substantial additional benefit of empagliflozin in combination with other cardiovascular risk factor medications for combination with one or more hypoglycaemic agents for patients with established cardiovascular disease. Based on these results, empagliflozin was therefore additionally designated as part of the appropriate comparator therapy in these patient groups for patients with established cardiovascular disease. Established cardiovascular disease was operationalized according to the inclusion criteria of the EMPA-REG Outcome Study as at least one of the following conditions: confirmed myocardial infarction, clinically relevant single-vessel coronary disease with ≥ 50% stenosis, multivessel coronary disease, unstable angina pectoris with angiographic evidence of coronary artery disease, ischemic or haemorrhagic stroke, or peripheral arterial occlusive disease with clinically relevant circulatory impairment, see study protocol, Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in diabetes type 2 N Engl J Med 2015; 373: 2117-28. DOI: 10.1056/NEJMoa1504720.

Furthermore, the IQWiG Rapid Report on the long-term cardiovascular study LEADER is available for liraglutide. Based on these positive study results on cardiovascular endpoints, the G-BA concluded that liraglutide in addition to at least one other hypoglycaemic agent is to be considered appropriate for patients with diabetes mellitus type 2 with established cardiovascular disease and further medication for the treatment of cardiovascular risk factors[3]. Established cardiovascular disease was operationalized according to the inclusion criteria of the LEADER study as at least one of the following conditions: confirmed myocardial infarction, confirmed stroke or transient ischemic attack, clinically relevant arterial occlusive disease or revascularisation, coronary artery

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

Courtesy translation – only the German version is legally binding.

disease, confirmed unstable angina pectoris, chronic renal failure (eGFR[8] ≤ 60 ml/min/1.73m^2) or chronic heart failure (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.

Long-term safety data on the other active ingredients or groups of active ingredients approved in the therapeutic indication are currently lacking; these are therefore not considered as appropriate comparator therapy in the present assessment procedure.

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

It is assumed that anti-diabetic therapy is initially started with metformin monotherapy. If metformin is not suitable due to contraindications/ intolerance, sulfonylureas should be used.

For patient group "b)" *(adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with* one hypoglycaemic agent (other than insulin) do *not adequately control blood glucose)*, human insulin may be used as a therapeutic option in individual cases in patients for whom metformin is intolerant or contraindicated according to the product information. As the overall patient group is small, no separate appropriate comparator therapy will be determined.

For patient group "c)" *(adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with at least two* hypoglycaemic agents (other than insulin) do not adequately control blood glucose): a multiple combination with three or more hypoglycaemic active ingredients is critically discussed due to poor controllability and an increased risk of drug interactions and side effects, so that in this therapy situation an insulin therapy in combination with metformin, with empagliflozin[4] or with liraglutide[4] is indicated. If metformin, empagliflozin and liraglutide are intolerable or contraindicated according to the product information or are not sufficiently effective due to advanced diabetes mellitus type 2 and a combination with insulin is not an option, human insulin alone is the appropriate comparator therapy.

In the anti-diabetic therapy situation of patient group "d)" *(adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose)*, optimisation of the human insulin regimen (if appropriate + metformin or empagliflozin[4] or liraglutide[4]) is determined to be the appropriate comparator therapy. The optimisation of the insulin therapy should take place in the form of a conventional insulin therapy (mixed insulin) or an intensified conventional insulin therapy, taking into account the individual life situation of the patient. In the context of ICT, the administration of an additional hypoglycaemic agent is not usually considered indicated.

It is assumed that for the treatment of comorbidities in patients with diabetes mellitus type 2 (such as hypertonia, dyslipoproteinaemia, CHD, etc.) a patient-specific treatment of the respective comorbidities, in particular by anti-hypertensive drugs, 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 disease of diabetes mellitus type 2.

According to the current generally recognised state of medical knowledge, there are neither advantages nor disadvantages for insulin analogues compared to human insulin,

[8] eGFR: estimated glomerular filtration rate.

Courtesy translation – only the German version is legally binding.

but there are no long-term data with advantages regarding hard endpoints for insulin analogues. The benefit assessment also considers evidence from studies in which insulin analogues were used, provided that the results from studies with insulin analogues are transferable to human insulin. The authorisation status of the insulin analogues must be taken into account. Study results should be examined for possible effect modification by the type of insulin used if the studies were conducted with both human insulin and insulin analogues.
However, when comparing costs, the treatment costs for human insulin must be taken into account, as this was determined to be the appropriate comparator therapy.

Insulin glargine is an insulin analogue that was not explicitly named as a component of the appropriate comparator therapy, but it is nevertheless accepted as a suitable comparator in view of the current data basis.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of semaglutide assessed as follows:

a) Adult patients with diabetes mellitus type 2 for whom diet and exercise alone do not adequately control blood glucose and for whom the use of metformin is not appropriate due to intolerance

a1) in patients without established cardiovascular disease[2]

An additional benefit is not proven.

a2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[9]

An additional benefit is not proven.

b) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with one hypoglycaemic agent (other than insulin) do not adequately control blood glucose

b1) in patients without established cardiovascular disease[2]

An additional benefit is not proven.

b2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

An additional benefit is not proven.

c) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with at least two hypoglycaemic agents (other than insulin) do not adequately control blood glucose

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

Courtesy translation – only the German version is legally binding.

c1) in patients without established cardiovascular disease[2]

An additional benefit is not proven.

c2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

An additional benefit is not proven.

d) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose

d1) in patients without established cardiovascular disease[2]

An additional benefit is not proven.

d2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

An additional benefit is not proven.

Cross-patient Aspects

For the renewed benefit assessment according to § 35a SGB V of semaglutide in adult patients with diabetes mellitus type 2 and high cardiovascular risk, the pharmaceutical company submitted the studies SUSTAIN 6 and PIONEER 6 in the dossier. The SUSTAIN 6 study was already available for the initial evaluation of semaglutide.

The SUSTAIN 6 and PIONEER 6 studies included patients with inadequately controlled diabetes mellitus type 2 and established cardiovascular disease and risk factors for cardiovascular disease[2] and had different pre-treatments. The study medication in the intervention and comparator arm was given in addition to a so-called standard therapy of diabetes mellitus type 2 and other cardiovascular risk factors and comorbidities. Due to the study design, the respective overall populations include patients with different comparator therapies. These cannot be divided into the different patient populations according to the specifications of the G-BA for the corresponding patient groups as well as the comparator therapy options defined in each case. Therefore, an assessment of the two studies SUSTAIN 6 and PIONEER 6 can only be made across the patient groups b2, c2 and d2 together.

SUSTAIN 6 study

The SUSTAIN 6 study is a randomised, placebo-controlled, double-blind, multicenter study conducted in North America, Latin America, Europe, Asia, and the countries of Algeria, Australia, Israel, and Turkey. The SUSTAIN 6 study included adult patients with diabetes mellitus type 2 with an HbA1c value ≥ 7.0% and with established cardiovascular disease or with at least one risk factor for cardiovascular disease. This was defined as follows. Patients aged 50 years and older had to have established cardiovascular disease with at least one of the following criteria: previous myocardial infarction, stroke or transient ischemic attack, revascularisation, > 50% stenosis, previous symptomatic coronary artery disease or unstable angina, asymptomatic cardiac ischemia, chronic heart failure (NYHA[10]-Class II-III) or chronic

[10] NYHA: New York Heart Association

Courtesy translation – only the German version is legally binding.

renal failure (eGFR[8] < 60 ml/min/1.73 m²). In patients 60 years of age and older, at least one risk factor for cardiovascular disease had to be present if at least one of the following conditions was met: Microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or Ankle Brachial Index < 0.9. Approximately 83% of all patients had a proven cardiovascular disease, the remaining 17% had at least one risk factor for this disease[2]. With regard to anti-diabetic therapy, both therapy-naïve and pretreated patients were included. The administration of GLP-1 receptor agonists or pramlintide 90 days before screening or DPP-4 inhibitors within 30 days before screening was not authorised.

A total of 3297 patients were randomised in a 1:1:1:1 ratio to the treatment arms semaglutide (subcutaneous: 0.5 mg or 1.0 mg) and placebo (subcutaneous: 0.5 mg or 1.0 mg), each of which was administered in addition to existing anti-diabetic therapy. The dose was initially 0.25 mg in all treatment arms and was increased to 0.5 mg after 4 weeks. After further 4 weeks, the 1.0 mg treatment arms were dosed up to 1.0 mg. No further dose adjustment of semaglutide or placebo was allowed.

According to the study protocol, the insulin dose should be reduced by 20% at baseline if the HbA1c value is ≤ 8.0% and should not be increased during the first 12 weeks. This affected 17% of patients in the semaglutide arm and 19% in the comparator arm. In patients with an HbA1c value above 8.0%, a dose reduction of insulin was allowed if an increase in hypoglycaemia was observed.

To meet glycemic targets (as specified in the *Standards of Medical Care in Diabetes*[11] or according to local clinical practice), other concomitant anti-diabetic medication was allowed to be adjusted at the discretion of the physician. Other concomitant anti-diabetic therapies were allowed to be added for adjunctive therapy if it was deemed necessary. However, GLP-1 receptor agonists, DPP-4 inhibitors, and pramlintide should be avoided. To ensure optimal glycemic control in all patients, an information notice was sent to all study sites via a newsletter in June 2013 and December 2014, specifying a glycemic target of 7.0% (taking into account individual patient needs) or referring to the treatment recommendations according to the ADA[12] and the EASD[13]. If the HbA1c value was still above 7.0% after 3 months, therapy should be intensified[14]. For the treatment of cardiovascular risk factors, adequate therapy should be used according to the study documents, especially anti-hypertensives, anticoagulants and lipid-lowering agents, which are based on current target values.

The primary endpoint of the study was time to first occurrence of any of the following events of the combined endpoint *major adverse cardiovascular events* (MACE): cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. The study duration was event- and time-controlled until at least 122 patients had reached the primary combined endpoint of MACE and at least 104 weeks after inclusion of the last study participant. The pre-specified event rate of 122 MACE events was reached early, so that all patients remained in the study for 109 weeks (104 weeks of treatment + 5 weeks of follow-up).

Patient characteristics were balanced between treatment groups. The average age of the patients was 65 years, about 60% of them were male. Only about 19 % of all patients included can be assigned to the European region. At baseline, the average HbA1c level was 8.7% and the average duration of diabetes in the patients was about 14 years.

---

[11] American Diabetes Association. Standards of medical care in diabetes: 2012. Diabetes Care 2012; 35(Suppl 1): S11-S63

[12] American Diabetes Association. Standards of medical care in diabetes: 2013. Diabetes Care 2013; 36(Suppl 1): S11-S66

[13] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach; position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012; 55(6): 1577-1596

[14] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016; 375(19): 1834-1844

Courtesy translation – only the German version is legally binding.

At baseline, almost all patients (98%) were receiving anti-diabetic therapy. Of these, about 58% of patients were treated with insulin (in combination with oral anti-diabetic drugs (OAD), if necessary) and about 84% were treated with other hypoglycaemic agents. Metformin was given to about 73% of patients and sulfonylureas were given to more than 40% of patients. The mean systolic blood pressure at baseline was approximately 136 mmHg. Almost all patients (about 98%) therefore received concomitant cardiovascular treatment. About 93% of patients received anti-hypertensive drugs and 76% each took lipid-lowering agents or antithrombotic drugs.

PIONEER 6 Study

The PIONEER 6 study is a randomised, placebo-controlled, double-blind study conducted in a multicenter setting in North and South America, Europe, Asia and Africa. Also in this study, adult patients with diabetes mellitus type 2 and with established cardiovascular disease or with at least one risk factor for cardiovascular disease were included. This was defined as follows. Patients aged 50 years and older had to have established cardiovascular disease with at least one of the following criteria: previous myocardial infarction, stroke or transient ischemic attack, revascularisation, > 50% stenosis, previous symptomatic coronary artery disease or unstable angina, asymptomatic cardiac ischemia, chronic heart failure (NYHA[15]-class II-III) or chronic renal failure (eGFR zw. 30-59 ml/min/1.73 m²). In patients 60 years of age and older, at least one risk factor for cardiovascular disease had to be present if at least one of the following conditions was met: Microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or Ankle Brachial Index < 0.9. Overall, 85% of all patients in the PIONEER 6 study had established cardiovascular disease, and the remaining 15% had at least one risk factor for it[2].

In the PIONEER 6 study, a total of 3183 patients were randomised in a 1:1 ratio to receive either once-daily oral semaglutide or placebo, each in addition to their existing anti-diabetic therapy. The dose of semaglutide was 3 mg daily in weeks 1 to 4, 7 mg daily in weeks 5 to 8, and then adjusted to your maintenance dose of 14 mg. Dose adjustments (dose reduction or extension of escalation phase for unacceptable AEs; re-escalation after resolution of AEs) were possible in the PIONEER 6 study.

With regard to anti-diabetic therapy, both treatment-naïve and pretreated patients were included in the PIONEER 6 study; however, GLP-1 receptor agonists, DPP-4 inhibitors, and pramlintide were not allowed within 90 days prior to study entry and throughout the treatment period. The glycaemic targets that should be achieved in the study are specified in *Standards of Medical Care in Diabetes*[16] or according to local clinical practice. Investigators were also informed in writing of the glycaemic target HbA1c value of 7.0% (or patient-specific target values taking into account individual patient needs). Concomitant anti-diabetic medication could be adjusted or additional anti-diabetic drugs added at the discretion of the physician, according to the respective local therapeutic standard and taking into account the local authorisation status. To avoid hypoglycaemia, the insulin dose should be reduced by approximately 10% to 20% at the beginning of the PIONEER 6 study.

For the treatment of cardiovascular risk factors, according to the study documents, adequate therapy of cardiovascular risk factors should be provided according to local standards as assessed by the investigators and should be based on current target values (e.g. blood pressure of 140/90 mmHg).

Also in the PIONEER 6 studies, the primary endpoint was time to first occurrence of one of the following events of the combined endpoint *major adverse cardiovascular events* (MACE): cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. The study duration was planned to be event-driven only and ended when 122 patients reached the primary combined

[15] NYHA: New York Heart Association

[16] American Diabetes Association. Standards of medical care in diabetes: 2012. Diabetes Care 2012; 35(Suppl 1): S11-S63

Courtesy translation – only the German version is legally binding.

endpoint of MACE. The median treatment duration was 62 weeks, and the median observation duration was 70 weeks.

Patient characteristics were comparable between the two treatment groups. The average age of the patients was 66 years and almost 70% of them were male. Approximately 17.5%of all included patients belong to the region of Western Europe. At baseline, the average HbA1c level was 8.2% and the average duration of diabetes in the patients was about 15 years.

In the PIONEER 6 study, approximately 61% of patients were receiving insulin therapy (possibly in combination with oral anti-diabetic drugs (OAD)) at baseline. In 78% of the patients, treatment was with metformin, in approx. 32 % with sulfonylureas. The mean systolic blood pressure at baseline was about 136 mmHg and about 94% of patients were receiving anti-hypertensive drugs. Furthermore, about 85% received lipid-lowering agents and about 79% antithrombotic drugs.

Suitability of the studies SUSTAIN 6 and PIONEER 6 for the benefit assessment

Both studies have methodological limitations in different aspects, which are described below:

Implementation of the appropriate comparator therapy

In his dossier, the pharmaceutical company presents the studies SUSTAIN 6 and PIONEER 6 for a research question defined by him on the treatment of patients with diabetes mellitus type 2 with high cardiovascular risk with semaglutide in addition to standard therapy compared to standard therapy. A separate presentation of results for all of the questions of the G-BA presented in section "2.1.2 *Appropriate comparator therapy"* is not provided.

Adult patients with diabetes mellitus type 2 and high cardiovascular risk represent a sub-population of patients covered by the therapeutic indication of semaglutide. According to the G-BA's stipulation, the additional benefit must be demonstrated for all patient groups compared to the specific appropriate comparator therapy. However, the pharmaceutical company does not submit evaluations that include all patient groups.

Irrespective of this, the SUSTAIN 6 and PIONEER 6 studies are also not fully suitable for the comparison of semaglutide versus standard therapy intended by the pharmaceutical company:

According to the study protocol, the blinded investigators of both studies should adjust the anti-diabetic medication to achieve optimal glycaemic control on a patient-by-patient basis according to the treatment recommendations. In this context, the investigators in both studies were reminded several times of the glycaemic target value of 7.0%, which takes into account individual patient needs, as well as the applicable therapy recommendations of the ADA and EASD. During the course of the SUSTAIN 6 study, 20.1% of patients in the semaglutide arm received additional anti-diabetic therapy, while the proportion of patients in the comparator arm was twice as high (40.6%). Of these, insulin therapy was initiated or adjusted in 9.4% of patients in the semaglutide arm compared to 24.0% in the comparator arm.
In the PIONEER 6 study, approximately 46% of patients in the semaglutide arm and approximately 49% of patients in the comparator arm received an adjustment or initiation of insulin therapy (regardless of duration or dose), with approximately 11% of patients in the semaglutide arm and approximately 24% of patients in the comparator arm receiving an adjustment or initiation of insulin therapy that was taken for > 21 days or corresponded to a dose increase of > 20%.

In terms of optimizing therapy with hypoglycaemic agents other than insulin, approximately 13% of patients in the semaglutide arm and approximately 24% of patients in the comparator arm in the SUSTAIN 6 study received an adjustment or initiation of anti-diabetic drugs other than insulin during the course of the study. More patients in the comparison group were also treated with these blood glucose-lowering therapies than with semaglutide.
In the PIONEER 6 study, treatment was adjusted or initiated with metformin and with sulfonylureas (approximately 14-15% in each of the two study arms).

Courtesy translation – only the German version is legally binding.

In view of the fact that the patients included in the two studies had a high cardiovascular risk or established cardiovascular disease, it is questionable whether the standard anti-diabetic therapy carried out in the studies corresponds to a recommended treatment of diabetes mellitus according to the current state of medical knowledge. Especially in patients with diabetes mellitus type 2 and established cardiovascular disease, treatment with liraglutide or empagliflozin has been shown to have a positive effect in preventing death. According to currently valid guidelines[17] and also in the recently published partial publication of the National Health Care Guideline for Type 2 Diabetes[18] the active ingredients liraglutide and empagliflozin, both of which were determined by the G-BA to be part of the appropriate comparator therapy, particularly in patients with established cardiovascular disease, are explicitly recommended for patients at high cardiovascular risk or with established cardiovascular disease. However, in both the SUSTAIN 6 and PIONEER 6 studies, GLP-1 receptor agonists (such as liraglutide) were not allowed or should be avoided. Overall, only 3 (< 1%) vs 8 patients (< 1%) received a GLP-1 receptor agonist during the course of the PIONEER 6 study and 23 (1.4%) vs 16 patients (1.0%) received a GLP-1 receptor agonist during the course of the SUSTAIN 6 study (both in the semaglutide vs control arm). With regard to treatment with SGLT-2 inhibitors, including empagliflozin, it appears that prior to the start of the PIONEER 6 study, approximately 9-10% of patients were already receiving SGLT-2 inhibitors, and 71 patients (4%) in the semaglutide arm and 133 patients (8%) in the comparator arm received initiation or adjustment of SGLT-2 inhibitor therapy. In contrast, in the SUSTAIN 6 study, which was completed 2.5 years earlier (2016), significantly fewer patients received SGLT-2 inhibitors: at baseline, one patient (0.1%) in the semaglutide arm and 4 patients (0.2%) in the comparator arm, respectively. During the course of the study, 44 patients (2.7%) in the semaglutide arm and 93 patients (5.6%) in the comparator arm, respectively, received initiation of therapy with SGLT-2 inhibitors[19].

In both studies, identical targets and escalation options of the anti-diabetic concomitant therapy were specified, so that it would have been expected that a correspondingly comparable reduction of the HbA1c value or at least an extensive approximation between the intervention semaglutide and the control would occur within the first study year. However, the reduction in HbA1c was significantly greater in the semaglutide arm compared with the control arm in both studies. Overall, patients had a mean HbA1c of approximately 7.2% and 7.4% in the semaglutide arms and 7.9% and 8.3% in the control arms of the PIONEER 6 and SUSTAIN 6 studies, respectively, at the end of treatment. Although the HbA1c target value specified in the studies was an individual target value to be aimed for, and it is therefore possible that for individual patients a target value above 7.0% was considered more suitable for medical reasons, it seems questionable whether this leads to the mean HbA1c value in the control arm being significantly higher than in the semaglutide arm. Although adjustments to anti-diabetic therapy were made in the control arm in both studies, overall it is unclear whether further adjustments to anti-diabetic therapy, particularly including liraglutide or empagliflozin, should have been made in the control arm during the course of the study in order to achieve the patients' target values.

Concomitant treatment of cardiovascular risk factors and comorbidities

In addition, data on blood pressure over the course of the study suggest that care regarding cardiovascular risk factors and cardiovascular disease was also inadequate and not implemented as specified in the study protocol. At baseline in both studies, approximately 35-40% of patients had systolic blood pressure above 140 mmHg. Blood pressure was reduced over the course of the study (approximately 25-30% in the semaglutide arms vs 30-35% in the control arms), showing differences between treatment groups in favour of semaglutide,

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

[18] National Health Care Guideline (NVL): Type 2 diabetes, partial publication of the long version - 2nd edition, version 1 https://www.leitlinien.de/mdb/downloads/nvl/diabetes-mellitus/diabetes-2aufl-vers1.pdf [published 25/03/2021]

[19] See also benefit assessment on semaglutide A18-75 dated 30 Jan 2019.

Courtesy translation – only the German version is legally binding.

although comparable blood pressure control between treatment groups would have been expected based on study guidelines.

Conclusion

Especially against the background of the further development of anti-diabetic therapy and taking into account the current guideline recommendations17,18which provide for the use of liraglutide or empagliflozin in patients with established cardiovascular disease or with a high cardiovascular risk, it would have been expected that the patients would have been increasingly treated with liraglutide or empagliflozin as part of the standard therapy carried out. Since these active ingredients, which were also determined by the G-BA as appropriate comparator therapy, were only used to a very limited extent, the study results cannot be transferred without restriction to the German health care context. Although adjustments to anti-diabetic and also antihypertensive therapy were made in both studies, overall it is assumed that further adjustments to anti-diabetic therapy (especially also with liraglutide or empagliflozin) and anti-hypertensive therapy in the control arm should have been made in the course of the study in order to achieve the patients' target values.

Despite the uncertainties, the studies SUSTAIN 6 and PIONEER 6 are included and assessed for the early benefit assessment according to Section 35a of the German Social Code, Book V due to the number of patients included, the patient-relevant endpoints investigated, especially with regard to cardiovascular events and all-cause mortality, although the studies are significantly shorter in terms of duration and size than, for example, the EMPA-REG and LEADER cardiovascular endpoint studies with a median observation period of approximately 2 and 1.5 years, respectively, and approximately 3,200 patients included.

On the results of the SUSTAIN 6 and PIONEER 6 studies:

Due to the heterogeneity of the study results of the SUSTAIN 6 and PIONEER 6 studies, no metanalytic summary of the respective endpoints was performed[20].

Mortality and morbidity

All-cause mortality/cardiovascular mortality

There were no significant differences between the treatment groups with respect to all-cause mortality and the endpoint "cardiovascular death" in the SUSTAIN 6 study.

Overall, 23 (1.4%) deaths occurred in the semaglutide arm and 45 (2.8%) deaths in the control arm (all-cause mortality) in the PIONEER 6 study. Regarding the endpoint "cardiovascular death", 15 (0.9%) deaths were recorded in the semaglutide arm and 30 (1.9%) deaths in the control arm. For both endpoints, the number of deaths was statistically significantly lower in the semaglutide arm than in the control arm.

Combined endpoint MACE

The combined endpoint "major adverse cardiovascular events (MACE)" covers the endpoints "cardiovascular death", "non-fatal myocardial infarction" and "non-fatal stroke" in both studies.

In the SUSTAIN 6 study, MACE showed a statistically significant difference in favour of semaglutide (HR 0.74, 95% CI [0.58; 0.95]; p=0.017). When looking at the individual components, there was a statistically significant advantage for semaglutide in the endpoint "non-fatal stroke" (HR 0.61; 95% CI [0.38; 0.99]; p=0.04). There were no statistically significant differences between the treatment arms in the other components "non-fatal myocardial infarction" and "cardiovascular death".

[20] See explanations in IQWiG's dossier assessment (A20-93), page 108f.

Courtesy translation – only the German version is legally binding.

In the PIONEER 6 study, the combined endpoint MACE is not interpretable because the effects of semaglutide on the individual components are not equidirectional. The results for the individual components are as follows: Regarding the endpoint "cardiovascular death", there is a statistically significant advantage for semaglutide. For the non-fatal stroke endpoint, numerically fewer strokes were observed in the semaglutide arm compared with the control arm (0.8% vs 1.0%). Regarding the endpoint "non-fatal myocardial infarction", more events occurred in the semaglutide arm compared to the control arm (2.3% vs 1.9%). However, there were no statistically significant differences between the treatment arms for either endpoint.

Other cardiovascular morbidity endpoints

For the endpoints of total fatal and non-fatal myocardial infarctions as well as strokes, hospitalisation due to heart failure and TIA[21] there were no statistically significant differences between the treatment groups in either study.

Complications of diabetic retinopathy

For the endpoints on complications of diabetic retinopathy, the endpoint "retinal photocoagulation" in the SUSTAIN 6 study showed a statistically significant disadvantage of semaglutide compared to the comparator arm (2.3% vs 1.2%). For the other individual endpoints "vitreous haemorrhage" and "diabetes-related blindness" only few events occurred and there was an direction of effect to the disadvantage of semaglutide, which, however, was not statistically significant in each case.

In the PIONEER 6 study, the endpoint "diabetic retinopathy" was not systematically recorded; therefore, no usable data for the benefit assessment are available.

Kidney disease

In the SUSTAIN 6 study, there were no statistically significant differences between the semaglutide arm and the comparator arm with respect to the endpoints "acute kidney injury", "kidney failure" and "initiation of permanent renal replacement therapy".

For the endpoint "acute kidney injury", there were no statistically significant differences between the treatment groups in the PIONEER 6 study. The operationalization of the endpoints "kidney failure" and "initiation of permanent renal replacement therapy" were not collected in the study; thus, no usable data for the benefit assessment are available.

Quality of life

SF-36v2

According to IQWiG's current methodological approach (Methods 6.0, published on 5.11.2021), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of exactly 15% of the scale range) to be necessary for patient-reported endpoints in order to represent a noticeable change with sufficient certainty.

In the SUSTAIN 6 study, there was no statistically significant difference between the treatment groups with regard to the results of the SF-36 with a response threshold of 15% of the scale range[22] for the physical and the mental sum score respectively.

In the PIONEER 6 study, the endpoint quality of life was not assessed; therefore, no usable data for the benefit assessment are available.

[21] TIA: transient ischemic attack

[22] corresponds to an improvement by the following values: physical sum score (PCS): ≥ 9.7 points, mental sum score (MCS): ≥ 9.6 points.

Courtesy translation – only the German version is legally binding.

Side effects

Serious adverse events (SAE)

In the PIONEER 6 and SUSTAIN 6 studies, there were no statistically significant differences between treatment groups for the endpoint of SAE in either study.

Therapy discontinuation due to AE

In the PIONEER 6 and SUSTAIN 6 studies, statistically significantly more patients discontinued therapy due to AEs in the semaglutide arm compared to the placebo arm (approximately 12-13% vs approximately 7%).

Hypoglycaemias

For the endpoints "severe hypoglycaemia" and "confirmed symptomatic hypoglycaemia (blood glucose limit ≤ 70 mg/dl)" endpoints, there were no statistically significant differences between the treatment arms in the SUSTAIN 6 study. For the endpoint "symptomatic hypoglycaemia (blood glucose limit < 56 mg/dl)", there are discrepant data between the current dossier and the dossier of 30 October 2018, so that the data cannot be used for the benefit assessment.

In the PIONEER 6 study, there were no statistically significant differences between treatment arms with respect to the endpoint of severe hypoglycaemia; symptomatic hypoglycaemia (blood glucose cut-off <56 or ≤70 mg/dl) was not recorded in the study.

Pancreatitis

In the PIONEER 6 and SUSTAIN 6 studies, there were no statistically significant differences between treatment groups for the endpoint of pancreatitis in either study.

Other specific AEs

For the endpoints gastrointestinal disorders (SOC[23]), as well as nausea, vomiting, diarrhoea and reduced appetite (PT[24]), there was a statistically significant difference in favour of semaglutide in the SUSTAIN 6 study.

These endpoints were not assessed in the PIONEER 6 study; therefore, no usable data for the benefit assessment are available.

In the SUSTAIN 6 study, there were no statistically significant differences between the treatment groups for the endpoint "injection site reactions".

As the PIONEER 6 study only investigated oral administration of semaglutide, this endpoint was not assessed.

Complementary endpoints

HbA1c

At baseline, patients in both study arms had a mean HbA1c of 8.7% (SUSTAIN 6) and 8.2% (PIONEER 6). By the end of treatment, HbA1c was reduced by 1.3% and 1.0% for patients in the semaglutide arm, compared to 0.4% and 0.3% for patients in the comparator arm. The difference between the treatment arms was not statistically significant. The endpoint "HbA1c" is a surrogate parameter and not *per se* relevant for patients.

Body weight

[23] SOC: System Organ Class.
[24] PT: preferred term

Courtesy translation – only the German version is legally binding.

At baseline, patients weighed an average of approximately 92 kg (SUSTAIN 6) and approximately 91 kg (PIONEER 6). By the end of treatment, body weight was reduced by an average of 4.2 kg in the semaglutide arm in both studies, compared with a reduction of 0.6 kg (SUSTAIN 6) and 0.8 kg (PIONEER 6) in the comparator arm. The difference between the treatment arms was not statistically significant. The endpoint "body weight" is also a surrogate parameter and not *per se* relevant to patients.

Overall assessment

For the evaluation of the additional benefit of semaglutide for the treatment of inadequately controlled diabetes mellitus type 2 in adults as an addition to diet and exercise, the SUSTAIN 6 and PIONEER 6 study were submitted. These studies included only diabetes mellitus type 2 patients and with established cardiovascular disease from the age of 50 years or with a high risk of cardiovascular disease from the age of 60 years[2]. Approximately 83-85% of all patients in the study had proven established cardiovascular disease, and the remaining 15-17% of patients were at risk for cardiovascular disease2. Against this background, statements can only be made for patients with diabetes mellitus type 2 with established cardiovascular disease, so that the studies can only be used to derive an additional benefit of semaglutide for patient groups b2, c2, d2.

The objective in both studies was to demonstrate the cardiovascular safety of semaglutide as measured by the combined endpoint MACE[25]. In the mortality category, there was a statistically significant advantage of semaglutide over standard therapy with regard to "all-cause mortality" and "cardiovascular mortality" in the PIONEER 6 study. In the SUSTAIN 6 study no statistically significant difference was detected between the treatment groups. With regard to the primary endpoint MACE, the SUSTAIN 6 study showed a statistically significant advantage of semaglutide compared to the comparison group, which is particularly due to the single component "non-fatal strokes". In the PIONEER 6 study, the combined endpoint MACE is not interpretable because the effects of semaglutide in the individual components are not equidirectional: For the endpoint "cardiovascular death", there is a statistically significant advantage for semaglutide, as already described. Regarding the endpoint "non-fatal stroke", as in the SUSTAIN 6 study, fewer strokes were recorded with semaglutide compared to the comparator arm, but the difference is not statistically significant. With respect to the endpoint of nonfatal myocardial infarction, numerically more events occurred in the semaglutide arm compared with the control arm in the PIONEER 6 study, whereas numerically more events occurred in the control arm in the SUSTAIN 6 study; however, the results in each case were not statistically significantly different between treatment groups. Quality of life was only assessed in the SUSTAIN 6 study, and overall no advantage or disadvantage can be derived from semaglutide.
In the SUSTAIN 6 study, a statistically significant difference to the disadvantage of semaglutide compared to control was recorded with regard to the endpoint "retinal photocoagulation". Endpoints on diabetic retinopathy were not collected in the PIONEER 6 study. In both studies, there was a statistically significant difference in the endpoints "therapy discontinuation due to AE" and "discontinuation due to gastrointestinal disorders" to the disadvantage of semaglutide compared to the comparator arm. Specific AEs such as gastrointestinal disorders, nausea, vomiting, diarrhoea, and decreased appetite were recorded exclusively in the SUSTAIN 6 study and also showed statistically significant differences to the disadvantage of semaglutide compared to the comparator arm. There were no statistically significant differences in the other endpoints.

The overall results of the PIONEER 6 and SUSTAIN 6 studies show advantages and disadvantages of semaglutide compared to the control group. The benefits shown in the PIONEER 6 study with regard to all-cause mortality and cardiovascular mortality, and in the SUSTAIN 6 study with regard to the endpoint MACE and non-fatal strokes, could not be

[25] Combined endpoint MACE consists of the individual components "cardiovascular death", "non-fatal stroke" and "non-fatal myocardial infarction".

Courtesy translation – only the German version is legally binding.

confirmed by the results of the other study. The results for therapy discontinuations due to AE (gastrointestinal disorders) are unfavourable for semaglutide in both studies; further disadvantages for retinal photocoagulation and gastrointestinal disorders are only evident in the SUSTAIN 6 study, whereby these endpoints were not assessed in the PIONEER 6 study. Due to the heterogeneous results of the two studies, the low extent and the questionable validity of the observed effects in the endpoint categories mortality and morbidity, as well as the clear disadvantages in the side effects, it is concluded, against the background of the described, relevant uncertainties of the studies, in particular with regard to the transferability to the German health care context and the lack of comparison with the appropriate comparator therapy in the respective patient group, that the additional benefit of semaglutide is not proven.

On the individual therapy regimens:

a) Adult patients with diabetes mellitus type 2 for whom diet and exercise alone do not adequately control blood glucose and for whom the use of metformin is not appropriate due to intolerance

a1) in patients without established cardiovascular disease2

An additional benefit is not proven.

Justification:

No study was presented to assess the additional benefit of semaglutide monotherapy when diet and exercise alone in adult patients with diabetes mellitus type 2 without established cardiovascular disease2 do not adequately control blood glucose and the use of metformin is considered inappropriate due to intolerance, compared with the appropriate comparator therapy (sulfonylureas: Glibenclamide or glimepiride) would have been appropriate.

a2) in patients with established cardiovascular disease2 in combination with further medication for the treatment of cardiovascular risk factors[3]

An additional benefit is not proven.

Justification:

No direct comparator studies were presented that could be used to assess the additional benefit of semaglutide monotherapy when diet and exercise alone in adult patients with diabetes mellitus type 2 with established cardiovascular disease2 do not adequately control blood glucose and the use of metformin is considered inappropriate due to intolerance, compared with the appropriate comparator therapy (sulfonylureas: glibenclamide or glimepiride in combination with further medication for the treatment of cardiovascular risk factors[3]) would have been suitable.

In the data required for an assessment of the additional benefit in patients with established cardiovascular disease[2] in combination with additional medication for the treatment of cardiovascular risk factors[3] SUSTAIN 6 and PIONEER 6 (see comments on cross-patient aspects and on the studies, pp 11 ff), the proportion of patients without anti-diabetic medication before the start of the study was less than 2 %. In addition, it is unclear to what extent the admission criterion "metformin intolerance or contraindication" was taken into account for these patients, or how large the proportion of patients was. Consequently, also for this reason, no significant data can be derived from the SUSTAIN 6 and PIONEER 6 studies for the assessment of the additional benefit of semaglutide in (anti-diabetic) monotherapy in patients with established cardiovascular disease[2] derived when diet and exercise alone do not adequately control blood glucose and the use of metformin is considered inappropriate due to intolerance.

Courtesy translation – only the German version is legally binding.

b) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with one hypoglycaemic agent (other than insulin) do not adequately control blood glucose

b1) in patients without established cardiovascular disease2

An additional benefit is not proven.

Justification:

For patient population b), the pharmaceutical company submits the direct comparator 2-arm, randomised, active controlled, unblinded PIONEER 2 study. This studied the administration of semaglutide versus emagliflozin (each in combination with metformin) for 52 weeks in 821 adults with diabetes mellitus type 2 who had inadequate glycemic control (HbA1c ≥ 7.0% and ≤ 10.5%) despite at least 90 days of pre-treatment with ≥ 1,500 mg/day of metformin. Patients were excluded if they had heart failure (NYHA[10]-Class IV), myocardial infarction, stroke, or hospitalisation for unstable angina pectoris or TIA within 180 days prior to study enrolment[21] and patients who were already scheduled for coronary, peripheral or carotid revascularisation at screening. Patients with cardiovascular disease or at high cardiovascular risk for whom none of these exclusion criteria were met were eligible for inclusion in the study.
The primary endpoint in the study was the change in HbA1c value after 26 weeks compared to baseline.

In the PIONEER 2 study, semaglutide and empagliflozin were administered according to a fixed escalation schedule up to the respective approved maximum dose. The dose of semaglutide was increased at 4-week intervals from 3 mg/day to 7 mg/day to the maximum approved dose of 14 mg/day. The starting dose of empagliflozin was 10 mg/day; this was increased to the maximum approved dose of 25 mg/day after 8 weeks if patients tolerated empagliflozin and had an eGFR[8] ≥ 60 ml/min/1.73 m². According to the product information of semaglutide and empagliflozin, the maximum doses should be used as an option if further blood glucose lowering or control is needed. However, no information is available on whether the PIONEER 2 study reviewed whether further improvement in glycaemic control or tighter glycaemic control was necessary for the patients in the study before increasing to the maximum dose.

Further adjustments to concomitant anti-diabetic treatment were allowed in the PIONEER 2 study for persistent unacceptable hyperglycaemia at the discretion of the investigator and according to local guidelines and standards. Information on what metformin dosage patients received in the PIONEER 2 study or whether dosage adjustment was made from ≥ 1500 mg/day to the locally approved maximum dosage, which is 3000 mg/day in Germany, is not available. The use of GLP-1 receptor agonists, DPP-4 inhibitors and amylin analogues in the intervention arm or SGLT-2 inhibitors in the comparison arm was not allowed.

In the PIONEER 2 study, patients had a mean age of 58 years; demographic and clinical characteristics were largely balanced between study arms. The mean HbA1c at baseline was 8.1% in both study arms, and the mean duration of diabetes was approximately 7.5 years. At study enrolment, 73% of patients had hypertonia, 13% had ischemic heart disease, and 7% had other cardiovascular diseases.

During the study period, about 15% of the patients received additional anti-diabetic medication; sulfonylureas were used most frequently (about 10%). Other additional anti-diabetic medications, such as insulin, were administered only sporadically during the course of the study. Overall, 18% of patients discontinued study medication in the semaglutide arm and 11% in the empagliflozin arm.

The cross-endpoint risk of bias is rated as low for the PIONEER 2 study. Due to the lack of blinding, the potential risk of bias for the endpoints health-related quality of life measured (SF-36v2), discontinuation due to AEs, symptomatic confirmed hypoglycaemia [PG < 56 mg/dl], genital infection, urinary tract infection, and other specific AEs is estimated as high and for all other endpoints as low.

Courtesy translation – only the German version is legally binding.

The PIONEER 2 study is particularly suitable for evaluating the additional benefit of semaglutide in patient group b1) combination therapy with another hypoglycaemic agents (other than insulin) in adult patients with diabetes mellitus type 2 *without* established cardiovascular disease2when diet and exercise alone do not adequately control blood glucose, compared with the appropriate comparator therapy (metformin in combination with empagliflozin). Since the exact proportion of patients with established cardiovascular disease2 is not known or the data indicate that the proportion is probably low is not known, or the data indicate that the proportion is probably low, the study is not used for the benefit assessment of patient group b2).

On the results of the PIONEER 2 study:

Mortality and morbidity

Overall mortality

Only one death occurred in the empagliflozin arm in the PIONEER 2 study. There were no significant differences between the treatment groups.

Acute coronary syndrome

Acute coronary syndrome was defined in the PIONEER 2 study as acute myocardial infarction, silent myocardial infarction, or hospitalisation for unstable angina pectoris; however, for silent myocardial infarction and hospitalisation for unstable angina pectoris, it remains unclear to what extent outcomes are influenced by incidental findings without symptomatology or the context of care. There is no information in the dossier on the number of patients with the individual events of the acute coronary syndrome component. Against this background, no usable data are available for the endpoint "acute coronary syndrome".

Cerebrovascular event

In the PIONEER 2 study, the endpoint "cerebrovascular event" includes the following adjudicated events: ischemic or haemorrhagic stroke, stroke with unexplained cause, or TIA[21]. Only four patients in the empagliflozin arm suffered a cerebrovascular event; although the difference is statistically significant in favour of semaglutide, no advantage can be derived due to the low number of events.

Hospitalisations for heart failure, kidney disease, and diabetic retinopathy

For the endpoints "hospitalisations due to heart failure" and "kidney disease", only few events occurred (maximum 2 per study arm). There were no significant differences between the treatment groups.

With regard to the endpoint "diabetic retinopathies", no usable data are available, as the PIONEER 2 study did not include a dedicated survey of diabetic retinopathies. However, the data submitted by the pharmaceutical company on the basis of pre-specified PTs on diabetic retinopathies and associated complications are not suitable to represent the endpoint diabetic retinopathies.

Quality of life

SF-36v2

According to IQWiG's current methodological approach (Methods 6.0, published on 5.11.2021), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of exactly 15% of the scale range) to be necessary for patient-reported endpoints in order to represent a noticeable change with sufficient certainty.

Courtesy translation – only the German version is legally binding.

In the PIONEER 2 study, there was no statistically significant difference between the treatment groups with regard to the results of the SF-36 with a response threshold of 15% of the scale range[26] for the physical and the mental sum score respectively.

Side effects

Serious adverse events (SAE)

SAEs occurred in 6.8% of patients in the semaglutide arm and 9% in the empagliflozin arm. There are no statistically significant differences between the treatment groups.

Therapy discontinuation due to AE

In the PIONEER 2 study, statistically significantly more patients discontinued therapy due to AEs in the semaglutide arm compared to the empagliflozin arm (approximately 10.7% vs 4.4%).

Hypoglycaemias

For the endpoints "severe hypoglycaemia" and "confirmed symptomatic hypoglycaemia (blood glucose ≤ 56 mg/dl)" endpoints, there were no statistically significant differences between the treatment arms in the PIONEER 2 study. For the endpoint "symptomatic hypoglycaemia (blood glucose < 70 mg/dl)", no data are available in the dossier. The pharmaceutical company submits this with the written statement, and it shows that in both study arms 5.4% of the patients had symptomatic hypoglycaemia (blood glucose < 70 mg/dl).

Acute pancreatitis

In the PIONEER 2 study, acute pancreatitis occurred in only one patient in each of the two study arms; there was no statistically significant difference between the treatment groups.

Other specific AEs

In the PIONEER 2 study, more patients in the semaglutide arm experienced gastrointestinal disorders (SOC[27]; 40.7% vs 14.2%) and nausea (PT[28]; 19.8% vs 2.4%) endpoints compared to the empagliflozin arm. The result is statistically significant to the disadvantage of semaglutide.

Regarding genital infections, statistically significantly more events were recorded in the empagliflozin arm (1.0% vs 7.6%), while urinary tract infections occurred with similar frequency in both study arms (approximately 3%). Diabetic ketoacidosis was experienced by only one patient in the empagliflozin arm. For the endpoints urinary tract infection and diabetic ketoacidosis, there were no statistically significant differences between the treatment groups.

Complementary endpoints

HbA1c

At baseline, patients had a mean HbA1c of 8.1%. By the end of the study at 52 weeks, HbA1c was reduced by 1.3% in patients in the semaglutide arm and by 0.9% in the empagliflozin arm. The difference is statistically significant. The endpoint "HbA1c" is a surrogate parameter and not *per se* relevant for patients.

Body weight

[26] corresponds to an improvement by the following values: physical sum score (PCS): ≥ 9.7 points, mental sum score (MCS): ≥ 9.6 points.
[27] SOC: System Organ Class.
[28] PT: preferred term

Courtesy translation – only the German version is legally binding.

At baseline, patients weighed an average of approximately 91.5 kg, and by the end of the study, body weight had decreased by an average of approximately 3.7 kg in both study arms. There are no statistically significant differences between the treatment groups. The endpoint "body weight" is also a surrogate parameter and not *per se* relevant to patients.

Overall assessment (patient population b1)

For patient population b, the direct comparator, unblinded PIONEER 2 study is available, which investigated the administration of semaglutide versus emagliflozin (in each case in combination with metformin) for 52 weeks in adults with diabetes mellitus type 2. Since the exact proportion of patients with established cardiovascular disease2 is not known, the study is particularly relevant for patient population b1).

Overall, few events occurred in the study for the endpoints of mortality and morbidity. Although there is a statistically significant advantage for semaglutide in the endpoint "cerebrovascular events" (0 vs 4 events), no advantage is derived due to the small number of events. With regard to quality of life, there are no advantages or disadvantages associated with semaglutide.

In the PIONEER 2 study, statistically significantly more patients discontinued therapy due to AE in the semaglutide arm compared to the empagliflozin arm and there were disadvantages under semaglutide for the endpoints "gastrointestinal disorders" and "nausea", whereas there were advantages under semaglutide compared to empagliflozin for the endpoint "genital infections" endpoint. The other side effect endpoints show no advantages or disadvantages of semaglutide compared with empagliflozin.

Overall, no advantage for semaglutide can be derived due to the low event rate for the endpoint "cerebrovascular events". In terms of side effects, there was a statistically significant increase in "therapy discontinuation due to AE" and "gastrointestinal disorders" with semaglutide, whereas there was an advantage with regard to "genital infections" compared to empagliflozin. Overall, it is concluded that an additional benefit of semaglutide + metformin compared with the appropriate comparator therapy empagliflozin + metformin in the patient population b1) adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with one hypoglycaemic agent (other than insulin) do *not* adequately control blood glucose *without* established cardiovascular disease[2] is not proven.

b2) in patients with established cardiovascular disease2 in combination with further medication for the treatment of cardiovascular risk factors[3]

An additional benefit is not proven.

Justification:
See comments on cross-patient aspects and on the PIONEER 6 and SUSTAIN 6 studies, pp. 11 ff.

For patient population b, the direct comparator, unblinded PIONEER 2 study is also available, which compared the administration of semaglutide over 52 weeks. Emagliflozin (in each case in combination with metformin) in adults with diabetes mellitus type 2. Since the exact proportion of patients with established cardiovascular disease2 is not known or the data indicate that the proportion is probably low is not known or the data indicate that the proportion is probably low, the study is not used for the benefit assessment of patient group b2).

Courtesy translation – only the German version is legally binding.

c) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with at least two hypoglycaemic agents (other than insulin) do not adequately control blood glucose

c1) in patients without established cardiovascular disease2

An additional benefit is not proven.

Justification:

No studies are available that would have been suitable for assessing the additional benefit of semaglutide in combination therapy with at least two hypoglycaemic agents (other than insulin) in adult patients with diabetes mellitus type 2 without high cardiovascular risk2, when diet and exercise alone do not adequately control blood glucose, would have been appropriate compared with the appropriate comparator therapy.

c2) in patients with established cardiovascular disease2 in combination with further medication for the treatment of cardiovascular risk factors[3]

An additional benefit is not proven.

Justification:
See comments on cross-patient aspects and on the PIONEER 6 and SUSTAIN 6 studies, pp. 11 ff.

d) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose

d1) in patients without established cardiovascular disease2

An additional benefit is not proven.

Justification:

No studies are available that would have been suitable for assessing the additional benefit of semaglutide in combination therapy with insulin in adult patients with diabetes mellitus type 2 without high cardiovascular risk2, when diet and exercise alone do not adequately control blood glucose, compared with the appropriate comparator therapy.

d2) in patients with established cardiovascular disease2 in combination with further medication for the treatment of cardiovascular risk factors[3]

An additional benefit is not proven.

Justification:
See comments on cross-patient aspects and on the PIONEER 6 and SUSTAIN 6 studies, pp. 11 ff.

Courtesy translation – only the German version is legally binding.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment for the new active ingredient semaglutide (Ozempic/Rybelsus) for the treatment of diabetes mellitus type 2 in adults.

In the therapeutic indication to be considered, four patient groups if respectively two subgroups were distinguished:

a) Adult patients with diabetes mellitus type 2 for whom diet and exercise alone do not adequately control blood glucose and for whom the use of metformin is not appropriate due to intolerance,

   a1) in patients without established cardiovascular disease[2]

   a2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

b) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with one hypoglycaemic agent (other than insulin) do not adequately control blood glucose,

   b1) in patients without established cardiovascular disease[2]

   b2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

c) Adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with at least two hypoglycaemic agents (other than insulin) do not adequately control blood glucose,

   c1) in patients without established cardiovascular disease[2]

   c2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

d) adult patients with diabetes mellitus type 2 for whom diet and exercise and treatment with insulin (with or without another hypoglycaemic agent) do not adequately control blood glucose,

   d1) in patients without established cardiovascular disease[2]

   d2) in patients with established cardiovascular disease[2] in combination with further medication for the treatment of cardiovascular risk factors[3]

Patient group a1)

The G-BA determined sulfonylureas (glibenclamide or glimepiride) to be the appropriate comparator therapy.

No studies are available for this patient group. Overall, the additional benefit of semaglutide compared to the appropriate comparator therapy for this patient group is not proven.

Patient group a2)

The G-BA determined sulfonylureas (glibenclamide or glimepiride) to be the appropriate comparator therapy.

No study is available that would have been suitable for the evaluation of the additional benefit of semaglutide as monotherapy in this patient group. Overall, the additional benefit of semaglutide compared to the appropriate comparator therapy for this patient group is not proven.

Patient group b1)

The G-BA determined the appropriate comparator therapy:

- Metformin and sulfonylureas (glibenclamide or glimepiride) or
- Metformin and empagliflozin or
- Human insulin, if metformin is intolerant or contraindicated according to the product information.

Courtesy translation – only the German version is legally binding.

For patient population b, the direct comparator, unblinded PIONEER 2 study is available, which investigated the administration of semaglutide versus emagliflozin (in each case in combination with metformin) for 52 weeks in adults with diabetes mellitus type 2. Since the exact proportion of patients with established cardiovascular disease2 is not known, the study is particularly relevant for patient population b1).

Overall, few events occurred in the study for the endpoints of mortality and morbidity. There is a statistically significant advantage for semaglutide in the endpoint of cerebrovascular events (0 vs 4 events), but no advantage is derived due to the small number of events. With regard to quality of life, there are no advantages or disadvantages associated with semaglutide. Regarding side effects, semaglutide had disadvantages for the endpoint discontinuation of therapy due to AE, gastrointestinal disorders and nausea endpoints, whereas semaglutide had advantages over empagliflozinforthe endpoint genital infections endpoint. For the other side effect endpoints as well as for the quality of life endpoint, there are no advantages or disadvantages of semaglutide compared to empagliflozin.

Overall, it is therefore concluded that an additional benefit of semaglutide compared to the appropriate comparator therapy is not proven.

Patient group b2)

The G-BA determined the appropriate comparator therapy:

- Metformin and sulfonylureas (glibenclamide or glimepiride) or
- Metformin and empagliflozin or
- Metformin and liraglutide[4] or
- Human insulin, if metformin is intolerant or contraindicated according to the product information.

The SUSTAIN 6 and PIONEER 6 studies were presented in which the administration of semaglutide compared to placebo (in each case for diabetic Standard therapy) in patients with diabetes mellitus type 2 and established cardiovascular disease[2] or risk factors for cardiovascular disease.

The overall picture shows advantages and disadvantages of semaglutide compared to the control. The benefits in terms of all-cause mortality or cardiovascular mortality (PIONEER 6) and in the endpoint of MACE and non-fatal strokes (SUSTAIN 6) could not be confirmed by the results of the other study. The results to the disadvantage of semaglutide in therapy discontinuations due to AE are shown in both studies; further disadvantages in retinal photocoagulation and gastrointestinal disorders are only shown in the SUSTAIN 6 study, whereby these were not recorded in the PIONEER 6 study.
Especially against the background of the further development of anti-diabetic therapy according to current guideline recommendations, it would have been expected that the patients would have been increasingly treated with liraglutide or empagliflozin within the framework of the standard therapy carried out. Although adjustments to anti-diabetic and anti-hypertensive therapy were made in both studies, overall it is anticipated that further adjustments to anti-diabetic therapy and anti-hypertensive therapy should have been made in the control arm during the course of the study to achieve the patients' target values.
Due to the heterogeneous results of the two studies, the low extent and the questionable validity of the observed effects with regard to mortality and morbidity, as well as the clear disadvantages with regard to side effects, it is concluded, against the background of the uncertainties of the studies described above, in particular with regard to the transferability to the German health care context and the lack of comparison with the appropriate comparator therapy, that the additional benefit of semaglutide is not proven.

Patient group c1)

The G-BA determined the appropriate comparator therapy:

Courtesy translation – only the German version is legally binding.

- Human insulin and metformin or
- only human insulin if metformin is intolerable or contraindicated according to the product information or is not sufficiently effective due to advanced diabetes mellitus type 2.

No studies are available for this patient group. Overall, the additional benefit of semaglutide compared to the appropriate comparator therapy for this patient group is not proven.

Patient group c2)

The G-BA determined the appropriate comparator therapy:

- Human insulin and metformin or
- Human insulin and empafliglozin[4] or
- Human insulin and liraglutide[4] or
- Human insulin if the specific combination partners are intolerable or contraindicated according to the product information or are not sufficiently effective due to advanced diabetes mellitus type 2.

The overall picture shows advantages and disadvantages of semaglutide compared to the control. The benefits in terms of all-cause mortality or cardiovascular mortality (PIONEER 6) and in the endpoint of MACE and non-fatal strokes (SUSTAIN 6) could not be confirmed by the results of the other study. The results to the disadvantage of semaglutide in therapy discontinuations due to AE are shown in both studies; further disadvantages in retinal photocoagulation and gastrointestinal disorders are only shown in the SUSTAIN 6 study, whereby these were not recorded in the PIONEER 6 study.
Especially against the background of the further development of anti-diabetic therapy according to current guideline recommendations, it would have been expected that the patients would have been increasingly treated with liraglutide or empagliflozin within the framework of the standard therapy carried out. Although adjustments to anti-diabetic and anti-hypertensive therapy were made in both studies, overall it is anticipated that further adjustments to anti-diabetic therapy and anti-hypertensive therapy should have been made in the control arm during the course of the study to achieve the patients' target values.
Due to the heterogeneous results of the two studies, the low extent and the questionable validity of the observed effects with regard to mortality and morbidity, as well as the clear disadvantages with regard to side effects, it is concluded, against the background of the uncertainties of the studies described above, in particular with regard to the transferability to the German health care context and the lack of comparison with the appropriate comparator therapy, that the additional benefit of semaglutide is not proven.

Patient group d1)

The G-BA determined the appropriate comparator therapy:

- The optimisation of the human insulin regime (+ metformin, if necessary)

No studies are available for this patient group. Overall, the additional benefit of semaglutide compared to the appropriate comparator therapy for this patient group is not proven.

Patient group d2)

The G-BA determined the appropriate comparator therapy:

- The optimisation of the human insulin regime (if necessary + metformin or empagliflozin[4] or liraglutide[4])

The overall picture shows advantages and disadvantages of semaglutide compared to the control. The benefits in terms of all-cause mortality or cardiovascular mortality (PIONEER 6) and in the endpoint of MACE and non-fatal strokes (SUSTAIN 6) could not be confirmed by the results of the other study. The results to the disadvantage of semaglutide in therapy discontinuations due to AE are shown in both studies; further disadvantages in retinal photocoagulation and gastrointestinal disorders are only shown in the SUSTAIN 6 study, whereby these were not recorded in the PIONEER 6 study.

Courtesy translation – only the German version is legally binding.

Especially against the background of the further development of anti-diabetic therapy according to current guideline recommendations, it would have been expected that the patients would have been increasingly treated with liraglutide or empagliflozin within the framework of the standard therapy carried out. Although adjustments to anti-diabetic and anti-hypertensive therapy were made in both studies, overall it is anticipated that further adjustments to anti-diabetic therapy and anti-hypertensive therapy should have been made in the control arm during the course of the study to achieve the patients' target values.
Due to the heterogeneous results of the two studies, the low extent and the questionable validity of the observed effects with regard to mortality and morbidity, as well as the clear disadvantages with regard to side effects, it is concluded, against the background of the uncertainties of the studies described above, in particular with regard to the transferability to the German health care context and the lack of comparison with the appropriate comparator therapy, that the additional benefit of semaglutide is not proven.

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

The information on the number of patients is based on the target population in statutory health insurance.

Despite the importance of the disease, the data basis regarding the published literature on the current prevalence and incidence of diabetes mellitus in Germany is limited and heterogeneous.

The G-BA considers the data from IQWiG's working paper on the determination of the SHI target population for the indication diabetes mellitus type 2 in the relevant therapy situations according to the third validation stage (https://www.iqwig.de/download/GA16-03_Routinedaten-bei-Diabetes-mellitus-Typ-2_Arbeitspapier_V1-1.pdf *[accessed 2021-03-25]*). The figures given in the working paper refer to the 2013 year. Due to the increasing prevalence in the indication diabetes mellitus type 2, more patients in total could fall into the target population in 2021.

The patient numbers considered include patients with validated (ie repeated) prescriptions of an active ingredient within the a year under consideration. This excludes all patients newly treated with anti-diabetics in the 4th quarter of the year under review as well as those who did not receive a second prescription of an active ingredient within the year under review. This aspect may also result in an underestimation of the number of patients in the target population.

Since there is a lack of follow-up observations on the basis of which conclusions can be drawn about the prescription consequences of anti-diabetic drugs in the course of the patients' disease, a proportion of the patients *in* the next therapy level is used to determine the number of patients *in* patient group c) *(patients for whom diet and exercise and treatment with at least two hypoglycaemic agents (other than insulin) do not sufficiently control blood glucose)*. This is in line with guideline recommendations in this therapeutic situation that basal-assisted oral therapy (BOT) may also be indicated in these patients. In principle, patients who receive monotherapy with basal insulin or monotherapy with bolus insulin are also considered here.

Overall, patient group c) includes, on the one hand, patients receiving a triple or multiple combination of anti-diabetic drugs (other than insulin) and, on the other hand, those patients receiving BOT, monotherapy with basal insulin and monotherapy with bolus insulin.

When determining the number of patients in patient group d) *(patients for whom diet and exercise and treatment with insulin (with or without another anti-diabetic agent)* are used, on the one hand, dual combinations of insulin and another anti-diabetic agent (here: metformin, sulfonylurea, another anti-diabetic agent) considered. These dual combinations include all possible types of insulin therapy (basal, bolus, CT, ICT, other insulin combinations). On the

Courtesy translation – only the German version is legally binding.

other hand, this patient group also includes those patients who receive monotherapy with insulin in the context of CT, ICT and other insulin combinations (except monotherapy with basal insulin, monotherapy with bolus insulin). Since patients who receive a two-drug combination of basal insulin and another anti-diabetic drug in the context of a BOT are also included in patient group c), a possible overestimation of patient numbers cannot be ruled out.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for rybelusus/ozempic (active ingredient: semaglutide) at the following publicly accessible link (last access: 19 January 2021):
https://www.ema.europa.eu/documents/product-information/rybelsus-epar-product-information_de.pdf

The use of GLP-1 receptor agonists (including semaglutide) has been associated with a risk of developing acute pancreatitis. Patients should be informed about characteristic symptomatology of acute pancreatitis, and therapy should be changed if necessary.

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 March 2021).

Treatment duration and consumption

With regard to consumption, the annual average consumption was determined by indicating the number of tablets or individual doses. The daily dosages recommended in the product information were used as a basis for calculation, and, if necessary, appropriate ranges were formed. The costs of a possibly necessary titration phase have not been shown, since the anti-diabetic therapy is a continuous long-term therapy and the titration is patient-specific.

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

For semaglutide (solution for injection), the starting dose is 0.25 mg administered subcutaneously once weekly. After four weeks, the dose should be increased to 0.5 mg once a week. The cost presentation of the combination therapies is based on the active strength 0.5 -1.0 mg. The oral dosage form of semaglutide is not on the market as of Lauer's update of 15 March 2021 and is therefore not used in the cost calculation.

For metformin, starting doses of 500 mg or 850 mg two to three times daily are recommended, but dose increases up to 3,000 mg metformin daily are possible; the total daily dose is usually divided into 2 - 3 doses. Therefore, an active strength of 1,000 mg metformin/tablet is used as the basis for the cost presentation.

Glibenclamide therapy should be started at 1.75 - 3.5 mg and increased to up to 10.5 mg glibenclamide per day if metabolic control is inadequate. The calculation is based on an active strength of 3.5 mg, as this dosage covers all the dosages recommended in the product information.

Therapy with glimepiride in combination with other oral antidiabetic agents should be started with a low initial dose and gradually increased to the maximum tolerated daily dose depending on the desired metabolic state. The recommended maximum dose is 6 mg, but according to the product information, glimepiride doses of more than 4 mg per day only improve the effect in isolated cases.

Courtesy translation – only the German version is legally binding.

For empagliflozin, a starting dose of 10 mg once daily is recommended as combination therapy with other hypoglycaemic agents, including insulin. If metabolic control is inadequate, the dose may be increased to 25 mg once daily. Therefore, both strength sizes are taken into account for the cost presentation.

The initial daily dose of liraglutide is 0.6 mg; after one week, this is increased to 1.2 mg. According to the product information, patients may benefit from a further increase in the dose from 1.2 mg to 1.8 mg. The appropriate dose of liraglutide is injected subcutaneously daily (pre-filled pen).

A variety of different insulin dosing regimens are available for insulin therapy. In addition, according to the insulin dosing regimen used, the amount of insulin and the frequency of application must be individually adjusted according to the patient's physical activity and lifestyle. To ensure comparability of costs, simplified assumptions have been made for the presentation of treatment duration and dosage. In the "Treatment duration" table, the treatment mode for human insulin (NPH insulin or mixed insulin) is shown as "1 - 2 x daily", although the frequency of application may differ for individual patients. According to the product information[29], the average insulin requirement is often 0.5 - 1.0 I.U. per kg body weight per day. The basal insulin daily requirement is usually 40 - 60% of the insulin daily requirement, the remaining requirement is covered accordingly by meal-dependent bolus insulin. Three main meals are assumed when calculating bolus insulin consumption. This information was used to calculate the dose of insulin per patient.

For the calculation of the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. Therefore, an average body weight of 77.0 kg is assumed for the bodyweight according to the official representative statistics "Microcensus 2017"[30].

Consequently, weight differences between women and men, as well as the fact that the bodyweight of patients with diabetes mellitus type 2 may be higher than the average 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)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Patient population a), b), c) and d)				
Semaglutide	continuously, 1 x daily	52	1	52
Patient population b)				
+ metformin or	continuously, 2-3 times a day	365	1	365
+ glibenclamide	continuously, 1-2 times a day	365	1	365

[29] Product information for Insuman® Basal, as of: April 2018.

[30] Statistisches Bundesamt (Federal Statistic Office), Wiesbaden 2.08.2018. Microcensus 2017: questions on health - body measurements of the population 2017 [online]. [Accessed: 13/09/2018): https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
or + glimepiride	continuously, 1 x daily	365	1	365
Patient population c)				
+ metformin	continuously, 2-3 times a day	365	1	365
+ glibenclamide or + glimepiride	continuously, 1-2 times a day continuously, 1 x daily	365 365	1 1	365 365
Patient population d)				
+ human insulin (NPH insulin)	continuously, 1-2 times a day	365	1	365
if necessary + metformin	continuously, 2-3 times a day	365	1	365
Appropriate comparator therapy				
Patient population a)				
Glibenclamide or	continuously, 1-2 times a day	365	1	365
Glimepiride	continuously, 1 x daily	365	1	365
Patient population b)				
Metformin	continuously, 2-3 times a day	365	1	365
Glibenclamide or	continuously, 1-2 times a day	365	1	365
Glimepiride	continuously, 1 x daily	365	1	365
Empagliflozin	continuously, 1 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365
Patient population c)				

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Human insulin (NPH insulin)	continuously, 1-2 times a day	365	1	365
Metformin	continuously, 2-3 times a day	365	1	365
Empagliflozin	continuously, 1 x daily	365	1	365
Liraglutide	continuously, 1 x daily	365	1	365
Conventional insulin therapy Mixed insulin	continuously, 1-2 times a day	365	1	365
Patient population d)				
Intensified conventional insulin therapy Human insulin (bolus insulin)	continuously, 3 x daily	365	1	365
Human insulin (NPH insulin)	continuously, 1-2 times a day	365	1	365
Conventional insulin therapy Mixed insulin	continuously, 1-2 times a day	365	1	365
if necessary + metformin	continuously, 2-3 times a day	365	1	365
if necessary + empagliflozin	continuously, 1 x daily	365	1	365
if necessary + liraglutide	continuously, 1 x daily	365	1	365

Courtesy translation – only the German version is legally binding.

Consumption:

Designation of the therapy	Dosage	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Patient populations a), b), c) and d)					
Semaglutide	0.5 mg 1 mg	0.5 mg 1 mg	1 x 0.5 mg 1 x 1 mg	52	52 x 0.5 mg 52 x 1 mg
Patient populations b), c) and d)					
+ metformin	500 mg 1,000 mg	1000 mg 3000 mg	1 x 1,000 mg 3 x 1,000 mg	365	365 x 1,000 mg 1095 x 1,000 mg
Patient populations b) and c)					
+ glibenclamide or	1.75 mg 7 mg / 3.5 mg	1.75 mg 10.5 mg	0.5 x 3.5 mg 3 x 3.5 mg	365	182.5 x 3.5 mg 1095 x 3.5 mg
+ glimepiride	1 mg 6 mg	1 mg 6 mg	1 x 1 mg 1 x 6 mg	365	365 x 1 mg 365 x 6 mg
Patient population d)					
+human insulin (NPH)	0,5. 1 I.U. per kg/KG	38,5. 77 I.U.	1 x 38,5 I.U. - 1 x 77 I.U.	365 365	14.052.5 I.U. - 28,105 I.U.
Appropriate comparator therapy					
Patient population a)					
Glibenclamide	1.75 mg 7 mg-3.5 mg	1.75 mg 10.5 mg	0.5 x 3.5 mg 3 x 3.5 mg	365	182.5 x 3.5 mg 1095 x 3.5 mg
Glimepiride	1 mg 6 mg	1 mg 6 mg	1 x 1 mg 1 x 6 mg	365	365 x 1 mg 365 x 6 mg
Patient population b)					
Metformin	500 mg 1,000 mg	1,000 mg 3,000 mg	1 x 1,000 mg 3 x 1,000 mg	365	365 x 1,000 mg - 1095 x 1,000 mg
+ glibenclamide	1.75 mg	1.75 mg	0.5 x 3.5 mg	365	182.5 x 3.5 mg

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Dosage	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
or	7 mg/3.5 mg	10, 5 mg	3 x 3.5 mg		1095 x 3.5 mg
+ glimepiride or	1 mg 6 mg	1 mg 6 mg	1 x 1 mg 1 x 6 mg	365	365 x 1 mg 365 x 6 mg
+ empagliflozin or	10 mg 25 mg	10 mg 25 mg	1 x 10 mg 1 x 25 mg	365	365 x 10 mg 365 x 25 mg
+ liraglutide	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365	365 x 1.2 mg 365 x 1.8 mg
Patient population c)					
Human insulin (NPH)	0,5. 1 I.U. per kg/KG	38,5. 77 I.U.	1 x 38,5 I.U. - 1 x 77 I.U.	365	14.052.5 I.U. - 28105 I.U.
+ metformin or	500 mg 1,000 mg	1,000 mg 3,000 mg	1 x 1,000 mg 3 x 1,000 mg	365	365 x 1,000 mg - 1095 x 1,000 mg
+ empagliflozin or	10 mg 25 mg	10 mg 25 mg	1 x 10 mg 1 x 25 mg	365	365 x 10 mg 365 x 25 mg
+ liraglutide	1.2 mg[22] - 1.8 mg	1.2 mg 1.8 mg	1 x 1.2 mg 1 x 1.8 mg	365	365 x 1.2 mg - 365 x 1.8 mg
Conventional insulin therapy Mixed insulin	0,5. 1 I.U. per kg/KG	38,5. 77 I.U.	1 x 38,5 I.U. - 1 x 77 I.U.	365	14.052.5 I.U. - 28,105 I.U.
Patient population d)					
Intensified conventional insulin therapy[31]	0,2.	15,4.	1 x 15,4 --	365	5,621 I.U. -

[31] 40 - 60% of the daily insulin requirement is usually covered by basal insulin; average insulin requirement: 0.5 - 1.0 I.U./kg body weight/day; reference: 77 kg body weight ("Microcensus 2017"); fast-acting insulin (bolus insulin) is also given at peak times.

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Dosage	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Human insulin (NPH insulin) +	0.6 I.U. per kg/KG	46.2 I.U.	1 x 46.2 I.U.		16,863 I.U.
Human insulin (bolus insulin)	0,2. 0.6 I.U. per kg/KG	15,4. 46.2 I.U.	1 x 15,4 -- 1 x 46.2 I.U.	365	5,621 I.U. - 16,863 I.U.
Conventional insulin therapy Mixed insulin	0,5. 1 I.U. per kg/KG	38,5. 77 I.U.	1 x 38,5 I.U. - 1 x 77 I.U.	365	14.052.5 I.U. - 28,105 I.U.
if necessary + metformin	500 mg 1,000 mg	1,000 mg 3,000 mg	1 x 1,000 mg 3 x 1,000 mg	365	365 x 1,000 mg - 1095 x 1,000 mg
if necessary + empagliflozin	10 mg 25 mg	10 mg 25 mg	1 x 10 mg 1 x 25 mg	365	365 x 10 mg 365 x 25 mg
if necessary + liraglutide	1.2 mg[22] - 1.8 mg	1.2 mg 1.8 mg	1 x 1.2 mg 1 x 1.8 mg	365	365 x 1.2 mg 365 x 1.8 mg

Costs:

Costs of the medicinal product:

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 Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

The fixed reimbursement rate was used as the basis for calculating the treatment costs for the active ingredient metformin, glibenclamide and glimepiride, human insulin and mixed insulin.

In the case of conventional insulin therapy, the costs for mixed insulin (i.e. a human insulin preparation in a specific mixing ratio of 30% normal insulin to 70% basal insulin) were used as a basis.

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Packaging 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					
Semaglutide 0.5 mg/1mg	12 ED	€ 290.32	€ 1.77	€ 15.46	€ 273.09
if necessary + metformin[32] 1.000 mg	180 FCT	€ 18.84	€ 1.77	€ 0.62	€ 16.45
if necessary + glibenclamide[32] 3.5 mg	180 TAB	€ 14.99	€ 1.77	€ 0.31	€ 12.91
if necessary + glimepiride 1 mg[32]	180 TAB	€ 16.93	€ 1.77	€ 0.47	€ 14.69
if necessary + glimepiride 6 mg[32]	180 TAB	€ 82.59	€ 1.77	€ 5.66	€ 75.16
if necessary + human insulin (NPH insulin)[32]	3000 I.U.	€ 89.70	€ 1.77	€ 6.22	€ 81.71
Appropriate comparator therapy					
Empagliflozin 10 mg	100 FCT	€ 192.40	€ 1.77	€ 10.04	€ 180.59
Empagliflozin 25 mg	100 FCT	€ 192.40	€ 1.77	€ 10.04	€ 180.59
Glibenclamide[32] 3.5 mg	180 TAB	€ 14.99	€ 1.77	€ 0.31	€ 12.91
Glimepiride 1 mg[32]	180 TAB	€ 16.93	€ 1.77	€ 0.47	€ 14.69
Glimepiride 6 mg[32]	180 TAB	€ 82.59	€ 1.77	€ 5.66	€ 75.16
Human insulin (bolus insulin) [32]	3000 I.U.	€ 89.70	€ 1.77	€ 6.22	€ 81.71
Human insulin (NPH insulin) [32]	3000 I.U.	€ 89.70	€ 1.77	€ 6.22	€ 81.71
Metformin[32] 1,000 mg	180 FCT	€ 18.84	€ 1.77	€ 0.62	€ 16.45
Mixed insulin[32]	3000 I.U.	€ 89.70	€ 1.77	€ 6.22	€ 81.71
Liraglutide 18 mg	100 – 150 ED	€ 570.70	€ 1.77	€ 30.99	€ 537.94
Abbreviations: ED = single doses; FCT = film-coated tablets, I.U. = International Units; TAB = Tablets					

LAUER-TAXE® last revised: 15 March 2021

Costs for additionally required SHI services:

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

[32] fixed reimbursement rate

Courtesy translation – only the German version is legally binding.

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 the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Costs for additionally required SHI services:

Designation of the therapy	Designation	Cost/package[33]	Number/	Consumption/year
Medicinal product to be assessed (semaglutide in combination with insulin (with or without oral antidiabetic agent))				
Human insulin (NPH insulin)	Blood glucose test strips	€ 18.50	1-3 times a day	365 – 1,095
	Lancets	€ 4.10	1-3 times a day	365 – 1,095
	Disposable needles	€ 22.80	1-2 times a day	365 – 730
Appropriate comparator therapy				
Human insulin (NPH insulin) and Conventional insulin therapy (mixed insulin)	Blood glucose test strips	€ 18.50	1-3 times a day	365 – 1,095
	Lancets	€ 4.10	1-3 times a day	365 – 1,095
	Disposable needles	€ 22.80	1-2 times a day	365 – 730
Intensified conventional insulin therapy	Blood glucose test strips	€ 18.50	4-6 times a day	1,460 – 2,190
	Lancets	€ 4.10	4-6 times a day	1,460 – 2,190
	Disposable needles	€ 22.80	4-5 times a day	1,460 – 1,825
Liraglutide	Disposable needles	€ 22.80	1 x daily	365

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.

[33] Number of test strips/pack = 50 pcs.; Number of lancets/pack = 200 pcs.; Number of disposable needles/pack = 100 pcs.; Presentation of the lowest-priced pack according to Lauer-Taxe, status: 15 March 2021

Courtesy translation – only the German version is legally binding.

4. Process sequence

At its session on 9 July 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 October 2020, the pharmaceutical company submitted a dossier for the benefit assessment of semaglutide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 2 November 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 semaglutide.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 January 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 February 2021. The deadline for submitting the written statements was 22 February 2021.

The oral hearing was held on 9 March 2021.

By letter of 10 March 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 26 March 2021.

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 7 April 2021, and the draft resolution was approved.

At its session on 15 April 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	09 July 2019	Determination of the appropriate comparator therapy
Working group Section 35a	03 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	09 March 2021 10 March 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 March 2021 31 March 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	7 April 2021	Concluding consultation of the draft resolution
Plenum	15 April 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Courtesy translation – only the German version is legally binding.

Berlin, 15 April 2021

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

Prof. Hecken

Courtesy translation – only the German version is legally binding.