Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Tirzepatide (type 2 diabetes mellitus)

of 2 May 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient tirzepatide on 15 November 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 13 November 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 February 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of tirzepatide compared with the appropriate comparator therapy could be determined on the basis of the dossier of the

pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure (and, if applicable, the addendum to the benefit assessment prepared by IQWiG). In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tirzepatide.

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 Approved therapeutic indication of Tirzepatide (Mounjaro) in accordance with product information

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

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

Therapeutic indication of the resolution (resolution of 2 May 2024):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) **Insulin-naïve** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

Appropriate comparator therapy for tirzepatide:

Patient-individual therapy, taking into account the patient-individual therapeutic goal, depending on comorbidities, diabetes duration, any risks of hypoglycaemia, under selection of:

- metformin + sulphonylureas (glibenclamide or glimepiride),
- metformin + sitagliptin,
- metformin + empagliflozin,
- Metformin + liraglutide

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

a2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

Appropriate comparator therapy for tirzepatide:

- metformin + empagliflozin, or
- metformin + liraglutide, or
- Metformin + dapagliflozin

b1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Appropriate comparator therapy for tirzepatide:

- metformin + empagliflozin + sitagliptin, or
- Metformin + empagliflozin + liraglutide

b2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Appropriate comparator therapy for tirzepatide:

- metformin + empagliflozin + liraglutide, or
- metformin + dapagliflozin + liraglutide

c1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is an indication for an insulin therapy**.

Appropriate comparator therapy for tirzepatide:

- Human insulin + metformin

c2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom there is an **indication for an insulin therapy**.

Appropriate comparator therapy for tirzepatide:

- human insulin + metformin + empagliflozin, or
- human insulin + metformin + dapagliflozin, or
- human insulin + metformin + liraglutide

d1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Appropriate comparator therapy for tirzepatide:

- Escalation of insulin therapy (conventional therapy (CT) if necessary + metformin or dulaglutide or intensified insulin therapy (ICT))

d2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Appropriate comparator therapy for tirzepatide:

- Escalation of insulin therapy: conventional therapy (CT) or intensified insulin therapy (ICT), in each case in combination with metformin and empagliflozin or dapagliflozin or liraglutide

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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 G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,

2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. The following active ingredients or product classes are approved for the treatment of adults with type 2 diabetes mellitus: Alpha-glucosidase inhibitors, dipeptidyl-peptidase-4 (DPP-4) inhibitors (gliptins), glinides, GLP-1 receptor agonists (glutides/ incretin mimetics), metformin, SGLT-2 inhibitors (gliflozins), sulphonylureas and insulin (human insulin, insulin analogues).

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 G-BA shall be preferred. Resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication type 2 diabetes mellitus in adults are:

- linagliptin (resolution of 21 February 2013; resolution of 16 May 2013),
- lixisenatide (resolution of 5 September 2013),
- saxagliptin/ metformin (resolution of 1 October 2013; resolution of 15 December 2016; resolution of 1 February 2018),
- vildagliptin (resolution of 1 October 2013; resolution of 21 May 2015),
- vildagliptin/ metformin (resolution of 1 October 2013),
- canagliflozin (resolution of 4 September 2014),
- insulin degludec (resolution of 16 October 2014; resolution of 20 August 2015; resolution of 16 May 2019),
- canagliflozin/ metformin (resolution of 5 February 2015),
- albiglutide (resolution of 19 March 2015),
- insulin degludec/ liraglutide (resolution of 15 October 2015; resolution of 4 February 2016),
- empagliflozin (resolution of 1 September 2016),
- empagliflozin/ metformin (resolution of 1 September 2016),
- saxagliptin (resolution of 15 December 2016),
- sitagliptin (resolution of 15 December 2016; resolution of 22 March 2019),
- sitagliptin/ metformin (resolution of 15 December 2016),

- insulin glargine/ lixisenatide (resolution of 16 August 2018; resolution of 15 October 2020),
- ertugliflozin/ sitagliptin (resolution of 1 November 2018),
- empagliflozin/ linagliptin (resolution of 22 November 2019),
- dapagliflozin (resolution of 19 December 2019),
- dapagliflozin/ metformin (resolution of 19 December 2019),
- dulaglutide (resolution of 16 July 2020),
- semaglutide (resolution of 15 April 2021).
- ertugliflozin (resolution of 19 May 2022).

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

It is assumed that pharmacotherapy is only started after failure of a sole basic therapy (non-medicinal measures such as diet, exercise, etc.) and is always carried out in combination with this.

In all guidelines relevant in the therapeutic indication, medicinal therapy with metformin is named as the standard in the care of patients with type 2 diabetes mellitus. It is assumed that anti-diabetic therapy is initially started with metformin monotherapy.

According to guideline recommendations, if glycaemic control is inadequate under metformin monotherapy, the administration of metformin is continued in the context of intensifying therapy with another medicine. In this respect, in the case of a possible abandonment of a treatment regimen with metformin, it must be explained in what way a therapy with metformin was not indicated for the patients.

Based on the results of cardiovascular Outcome studies and the recommendations of the guideline[2], which indicate that the most robust data were shown in diabetics with existing cardiovascular disease, a distinction is made between patients **with and without manifest cardiovascular disease** for the determination of the appropriate comparator therapy. The operationalisation for defining patients with manifest cardiovascular disease should be based on criteria that are generally recognised and established in medical science.

In **patient group a1**, taking into account the patient-individual therapeutic goal, depending on comorbidities, diabetes duration and any risks of hypoglycaemia, a patient-individual therapy is determined by selecting the active ingredients sulphonylureas (glibenclamide or glimepiride), sitagliptin, empagliflozin or liraglutide, in each case as a dual combination with metformin.

[2] National Health Care Guideline (NVL): Type 2 diabetes, long version - version 3.0, published on 15.05.2023 https://www.leitlinien.de/themen/diabetes/pdf/diabetes-vers3-0.pdf

In **patient group a1**, the sulphonylureas glibenclamide or glimepiride, which are classified as equivalent by the G-BA for the determination of the appropriate comparator therapy come into question. Glipizide is pharmacologically-therapeutically comparable to glimepiride in the group of sulphonylureas and is therefore accepted as a comparator in studies, according to previous resolutions in the field of type 2 diabetes mellitus.

For sitagliptin in the dual combination with metformin, positive study results are available from the P803, HARMONY 3 and P024 studies. For the dual combination sitagliptin with metformin, there was a hint for a minor additional benefit compared to the appropriate comparator therapy - determined in the resolution for sitagliptin - metformin in combination with sulphonylureas (glimepiride or glipizide) for all adults with type 2 diabetes mellitus and is therefore designated as part of the appropriate comparator therapy in the **patient group a1**.

For the dual combination empagliflozin with metformin, the 1245.28 study showed a hint for a minor additional benefit compared to the appropriate comparator therapy metformin in combination with sulphonylureas (glimepiride) for all adults with type 2 diabetes mellitus and is therefore designated as part of the appropriate comparator therapy in the **patient group a1**.

Furthermore, liraglutide is established in the care of insulin-naive patients with type 2 diabetes mellitus in particular; against this background, liraglutide is determined as part of the appropriate comparator therapy in **patient groups a1 and b1**.

In patients with manifest cardiovascular disease, there is, among others, evidence from cardiovascular endpoint studies on empagliflozin, liraglutide and dapagliflozin. The evidence on these active ingredients was taken into account in the early benefit assessment to derive an additional benefit or to determine the appropriate comparator therapy:

Positive study results are available for empagliflozin from the EMPA-REG Outcome study in adults with type 2 diabetes mellitus with manifest cardiovascular disease in combination therapy with other hypoglycaemic agents. Based on the EMPA-REG Outcome study, there was a hint for a considerable additional benefit of empagliflozin in combination with other medication for the treatment of cardiovascular risk factors for the combination with one or more hypoglycaemic agents for adults with type 2 diabetes mellitus and manifest cardiovascular disease. Based on these results, empagliflozin was therefore designated as part of the appropriate comparator therapy in these patient populations in each case for patients with manifest cardiovascular disease **(patient group a2, b2, c2, d2)**.

Furthermore, the IQWiG rapid report on the long-term cardiovascular LEADER study is available for liraglutide, which showed advantages in overall mortality, strokes and the composite endpoint MACE in adults with type 2 diabetes mellitus and manifest cardiovascular disease, as well as in patients with renal failure with an eGFR < 60 ml/min/1.73 m^2. Based on these positive study results on cardiovascular endpoints, the G-BA concluded that liraglutide in combination therapy with another or more hypoglycaemic agents is to be considered as another therapy option of the appropriate comparator therapy for adults with type 2 diabetes mellitus with established cardiovascular disease and further medication for the treatment of cardiovascular risk factors **(patient group a2, b2, c2, d2)**.

In addition, there are positive study results for dapagliflozin from the DECLARE-TIMI 58 study in adults with inadequately controlled type 2 diabetes mellitus and with increased cardiovascular risk or manifest cardiovascular disease. Based on the DECLARE-TIMI 58 study, a hint for a minor additional benefit of dapagliflozin in combination with other medication for the treatment of cardiovascular risk factors was derived for the combination with one or more hypoglycaemic agents for type 2 diabetics with increased cardiovascular risk. Patients with increased cardiovascular risk as well as patients with manifest cardiovascular disease were enrolled in the DECLARE-TIMI 58 study. In adults with type 2 diabetes mellitus and at high cardiovascular risk, as well as in those with manifest cardiovascular disease, the priority is to prevent a cardiovascular event. Therefore, the G-BA concluded that dapagliflozin is to be considered appropriate in addition to at least one other hypoglycaemic agent for patients with manifest cardiovascular disease (**patient group a2, b2, c2, d2**).

Sufficiently valid long-term safety data on the other active ingredients or product classes approved in the therapeutic indication are currently lacking, or an additional benefit could not be proven; these are therefore not considered as appropriate comparator therapy in the present assessment procedure.

In insulin-naive adults with type 2 diabetes mellitus, who have not achieved adequate glycaemic control with their current medicinal therapy consisting of two hypoglycaemic agents, in addition to diet and exercise, and for whom there is no indication for insulin therapy (**patient group b1, b2**), an insulin-free multiple combination consisting of metformin and two other active ingredients previously named as part of the appropriate comparator therapy is to be used (b1: empagliflozin, liraglutide, sitagliptin; b2: empagliflozin, dapagliflozin, liraglutide). If a third active ingredient is added, it should be checked whether this can achieve sufficient glucose lowering or whether the start of insulin therapy should be considered.

Human insulin has been shown to reduce diabetes-related microvascular complications[3].

The indication for insulin therapy should be carefully considered.

According to the guideline, an insulin therapy is[2] recommended in the following situations: if the individual therapeutic goal is not achieved despite intensification with other anti-diabetics, in the case of metabolic derailments, in the case of administration of diabetogenic medicines (e.g. glucocorticoids) and in the case of severely impaired renal function. The start of insulin therapy includes the administration of human insulin in combination with metformin (**patient group c1**) or human insulin in combination with metformin and another of the active ingredients named as part of the appropriate comparator therapy (empagliflozin, dapagliflozin, liraglutide) (**patient group c2**), in each case as part of a so-called basal supported oral therapy (BOT).

If insulin-dependent patients receiving BOT do not achieve adequate glycaemic control, the guideline recommends an escalation of insulin therapy as part of conventional insulin therapy (CT, mixed insulin) or intensified conventional insulin therapy (ICT), taking into account the individual life situation of the patients (**patient group d**). Escalation of insulin therapy is therefore determined as the appropriate comparator therapy in this patient group.

[3] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131):837-853

In insulin-dependent patients with inadequately controlled type 2 diabetes mellitus, positive results are available for dulaglutide in the AWARD-4 (without renal failure) and AWARD-7 (with moderate or severe renal failure) studies. In the corresponding sub-population of insulin-dependent adults, without or with renal failure, a hint for a minor additional benefit was derived in each case. Therefore, dulaglutide is determined for the patient population of insulin-experienced patients without manifest cardiovascular disease in the context of a CT as an additional therapy option of the appropriate comparator therapy, if necessary (**patient group d1**).

In addition to CT, metformin or dulaglutide may be administered, if necessary (**patient group d1**).

In adults with type 2 diabetes mellitus and manifest cardiovascular disease, treatment with metformin plus empagliflozin, liraglutide or dapagliflozin is the standard therapy. The guideline recommends continuing the initial therapy consisting of metformin and empagliflozin, liraglutide or dapagliflozin as part of the escalation of insulin therapy, provided that this therapy is well tolerated in combination with insulin. Consequently, it is assumed that this patient group generally receives therapy with metformin and empagliflozin or dapagliflozin or liraglutide in addition to conventional insulin therapy (CT) or intensified insulin therapy (ICT) (**patient group d2**).

Patients receiving insulin should be regularly checked to see whether the indication for insulin therapy still exists or whether de-escalation of insulin therapy is possible and indicated.

Sufficiently valid long-term safety data on the other active ingredients or product classes approved in the therapeutic indication are currently lacking, or an additional benefit could not be proven; these are therefore not considered as appropriate comparator therapy in the present assessment procedure.

It is assumed that for the treatment of comorbidities in adults with type 2 diabetes mellitus (such as hypertonia, dyslipoproteinaemia, CHD, kidney disease, etc.) and especially with existing manifest cardiovascular disease, who are receiving further medication for the treatment of cardiovascular risk factors, a patient-individual 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 present diseases.

According to the current generally recognised state of medical knowledge, there are neither advantages nor disadvantages for insulin analogues compared to human insulin, 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 and insulin lispro are insulin analogues that were not explicitly named as part of the appropriate comparator therapy, but these active ingredients are nevertheless accepted as a suitable comparator in view of the current data basis.

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

It is assumed that comparable therapy regimes are used in the intervention and comparator arms (fair comparison of the anti-diabetic agents used, dosages, etc.).

Change of the appropriate comparator therapy

The partial publication of the NVL - 2nd edition, version 1 from 2021 was used as the basis for determining the appropriate comparator therapy. In the version in question, the insulin therapy algorithm *(Figure 7)* did not contain any indication that the recommendation to escalate insulin therapy: *combination of basal insulin and short-acting insulin (possibly as mixed insulin) or intensified insulin therapy*, included an indication of simultaneous treatment with an SGLT-2 inhibitor or GLP-1-RA.

With the publication of the long version of the NVL - version 3.0 from 2023, the guideline group added a clarification to the recommendation for escalation of insulin therapy. Accordingly, patients who initially received a combination therapy of metformin and an SGLT-2 inhibitor or a GLP-1-RA after the indication for medicinal therapy was established are recommended to continue this therapy in combination with insulin as long as it is well tolerated. It is therefore assumed that patients with manifest cardiovascular disease generally receive therapy with metformin and empagliflozin or dapagliflozin or liraglutide in addition to conventional insulin therapy (CT) or intensified insulin therapy (ICT).

For this reason, the G-BA considers it appropriate to change the appropriate comparator therapy for the patient population d2. The appropriate comparator therapy is determined accordingly:

- Escalation of insulin therapy: conventional therapy (CT) or intensified insulin therapy (ICT), in each case in combination with metformin and empagliflozin or dapagliflozin or liraglutide.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of tirzepatide is assessed as follows:

a1) **Insulin-naïve** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

An additional benefit is not proven.

a2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

An additional benefit is not proven.

b1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

An additional benefit is not proven.

b2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

An additional benefit is not proven.

c1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is an indication for an insulin therapy**.

An additional benefit is not proven.

c2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom there is an **indication for an insulin therapy**.

An additional benefit is not proven.

d1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Hint for a minor additional benefit.

d2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

An additional benefit is not proven.

Justification:

Patient group a1)

For the assessment of the additional benefit of tirzepatide for the treatment of adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous therapy consisting of a hypoglycaemic agent, no studies were presented compared with the appropriate comparator therapy.

An additional benefit is therefore not proven.

Patient group a2)

For the assessment of the additional benefit of tirzepatide for the treatment of adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous therapy consisting of a hypoglycaemic agent, no studies were presented compared with the appropriate comparator therapy.

An additional benefit is therefore not proven.

Patient group b1)

For the assessment of the additional benefit of tirzepatide for the treatment of adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous therapy consisting of two hypoglycaemic agents - without insulin, no studies were presented compared with the appropriate comparator therapy.

An additional benefit is therefore not proven.

Patient group b2)

For the assessment of the additional benefit of tirzepatide for the treatment of adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous therapy consisting of two hypoglycaemic agents - without insulin, no studies were presented compared with the appropriate comparator therapy.

An additional benefit is therefore not proven.

Patient group c1)

For the assessment of the additional benefit of tirzepatide for the treatment of adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current therapy consisting of at least two hypoglycaemic agents and for whom insulin therapy is indicated for the first time, no studies were presented compared with the appropriate comparator therapy.

An additional benefit is therefore not proven.

Patient group c2)

For the assessment of the additional benefit of tirzepatide for the treatment of adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current therapy consisting of at least two hypoglycaemic agents and for whom insulin therapy is indicated for the first time, data from a sub-population of the SURPASS-4 study were presented.

SURPASS-4 study

SURPASS-4 is an open-label, randomised, active-controlled study with 4 parallel treatment arms. The study compared the administration of tirzepatide *(3 arms, 5 mg, 10 mg and 15 mg per week respectively)* versus insulin glargine (*1 arm*, *U100)*, in each case in addition to the previous oral hypoglycaemic therapy. The comparator treatment phase in the study lasted 52 weeks with a variable treatment phase from week 52 to week 104.

Population of the SURPASS-4 study

According to the inclusion criteria, patients should have an HbA1c value in the range of 7.5% to 10.5% at the time of enrolment in the study and an increased risk of cardiovascular events and a BMI ≥ 25 kg/m^2 despite at least 3 months of treatment with 1 to 3 oral antidiabetics in stable doses. An increased risk of cardiovascular events was operationalised as coronary artery heart disease; PAOD[4] or cerebrovascular disease, each with an atherosclerotic origin; chronic kidney disease or heart failure (NYHA[5] II - III) in conjunction with an age of ≥ 50 years. Exclusion criteria were defined as follows: Occurrence of myocardial infarction, stroke or hospitalisation due to heart failure within 2 months prior to enrolment in the study, or NYHA class IV heart failure.

According to the above inclusion and exclusion criteria, a total of 2,002 adults with type 2 diabetes mellitus were randomised to the 4 treatment arms *(approx. 330 subjects per tirzepatide arm versus 1,005 subjects in the insulin glargine arm)*. Previously, only metformin, SGLT-2 inhibitors and/or sulphonylureas were permitted as prior therapy.

Relevant for the early benefit assessment is the sub-population of adults who had received a combination therapy consisting of metformin and empagliflozin or metformin and dapagliflozin as pretreatment. For the relevant sub-population, this resulted in 107 patients in the intervention arms with tirzepatide compared with 122 sub-population in the comparator arm with insulin glargine. Around 90 % of the study participants had cardiovascular disease.

Treatment phase and target value-based titration based on fasting plasma glucose values

Three different doses of tirzepatide were investigated during the study: 5 mg, 10 mg and 15 mg. Allocation to the different tirzepatide arms with different doses was randomised. The starting dose of tirzepatide for all intervention arms was 2.5 mg once a week for a period of 4 weeks. The starting dose was then increased by 2.5 mg every 4 weeks according to a dose escalation regimen until the maintenance dose allocated at randomisation was reached. If intolerable gastrointestinal symptoms occurred with tirzepatide, the maintenance dose could be reduced once to the next lower dose (5 mg or 10 mg) in the first 24 weeks during the dose escalation phase. This lower dosage was then continued in the further course of the study. No further patient-individual dose adjustments of tirzepatide were planned.

In contrast, the study participants who were treated with insulin glargine (U100) in the comparator arm had to aim for a target value-oriented therapy with a fasting blood glucose target value of < 100 mg/dl. The dose of insulin glargine had to be continuously adjusted up to week 16 according to a predetermined titration regimen. With a fasting blood glucose value in the range of 71 to 99 mg/dl, no adjustment of the insulin dose was necessary. For values > 99 mg/dl, the dose of insulin glargine should be increased according to the titration protocol. This strict titration to the fasting blood glucose target value of < 100 mg/dl was only specified in the comparator arm.

In addition to the trial medication, the oral antidiabetics from the pretreatment were continued as concomitant antidiabetic medication in unchanged doses in all arms. For the sub-population, this was the dual combination of metformin with empagliflozin or dapagliflozin.

[4] PAOD = peripheral artery occlusive disease
[5] NYHA = New York Heart Association classes

With the exception of the trial medication in the intervention arms, however, the use of GLP-1-RA was not permitted. DPP-4 inhibitors and others were also not permitted.

The National Disease Management Guideline (NVL)[2] recommends the agreement of patient-individual HbA1c target values. Various factors such as age, physical condition, comorbidities, duration of diabetes, risk of hypoglycaemia, etc. should be taken into account. Depending on these personal factors, adults with type 2 diabetes mellitus benefit from different target values. This means that the individualisation of the HbA1c target value is of great importance in diabetes treatment.

In the SURPASS-4 study, however, no patient-individual HbA1c target values were agreed. Instead, the study participants in the intervention arms had to be randomly assigned to fixed doses of tirzepatide. This approach did not take into account the recommendation in the product information for tirzepatide that the tirzepatide dose can be further increased in 2.5 mg increments once the 5 mg maintenance dose has been reached. It is therefore unclear whether higher doses were actually medically indicated in the patients who received 10 mg or 15 mg tirzepatide. The implementation of strict target value-based titration of insulin glargine in the comparator arm to the specified fasting blood glucose target value of < 100 mg/dl is also not compatible with the standard procedure in German medical treatment practice. This specified titration is neither found in the product information for insulin glargine nor in the recommendations of the NVL. The practice recommendations of the German Diabetes Association also specify higher fasting blood glucose-target values from 100 to 125 mg/dl as a guide[6] for individually agreed therapy goals.

According to NVL[2], the indication for insulin treatment must be carefully checked before starting insulin therapy for the first time. If subjects with type 2 diabetes mellitus do not achieve their individual therapeutic goal with oral dual combination therapy and the requirements for an insulin indication are not met *(see above statements on appropriate comparator therapy)*, the NVL recommends intensification with an additional or alternative antidiabetic (other than insulin) for which positive effects on patient-relevant endpoints have been demonstrated. In the SURPASS-4 study, it was not checked in advance whether insulin therapy was actually medically indicated in the study participants who were allocated to the insulin glargine arm. For this reason, it cannot be conclusively assessed to what extent a triple combination therapy consisting of metformin + empagliflozin + liraglutide or metformin + dapagliflozin + liraglutide would not have been better indicated in the relevant sub-population in the comparator arm.

Even after assessing the data subsequently submitted in the written statement procedure[7] uncertainties remain as to whether the SURPASS-4 study actually involved guideline-compliant therapy based on patient-individual target values.

Overall, it can therefore be stated that the SURPASS-4 study has clear methodological uncertainties.

Due to the different treatment goals between the treatment groups with a strict insulin titration to a fasting blood glucose value of < 100 mg/dl, which was specified exclusively in the comparator arm, there is no fair comparison between the intervention and control arm. Based

[6] Landgraf R, Aberle J, Birkenfeld AL et al. Therapy of type 2 diabetes. Diabetology and Metabolism 2023; 18 (Supplement 2): S162-S217. https://doi.org/10.1055/a-2076-0024
[7] Addendum (A24-32) to IQWiG's dossier assessment (A23-11) on the active ingredient tirzepatide

on the SURPASS-4 study, it is therefore not possible to draw any conclusions about the additional benefit.

Taken together, the SURPASS-4 study is therefore unsuitable for the early benefit assessment. An additional benefit is not proven.

Patient group d1)

Data from the SURPASS-6 study were provided to assess the additional benefit of tirzepatide for the treatment of adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current insulin regimen.

SURPASS-6 study

SURPASS 6 is an open-label, randomised, active-controlled study with 4 parallel treatment arms. The study investigated the comparison of tirzepatide *(3 arms, each of 5 mg, 10 mg and 15 mg per week)* in combination with insulin glargine and possibly (±) metformin versus a combination of insulin glargine and insulin lispro ± metformin. The treatment phase lasted 52 weeks.

Population of the SURPASS-6 study

The SURPASS-6 study enrolled adults with type 2 diabetes mellitus who, despite a minimum 90-day insulin regimen consisting of a basal insulin in combination with up to 2 oral antidiabetics *(metformin, sulphonyl ureas, DPP-4 inhibitors)* had an HbA1c value in the range of 7.5% to 11%. A BMI of 23 to 45 kg/m^2 was also required for enrolment in the study. In principle, adults with cardiovascular disease or at high cardiovascular risk were able to participate. Explicitly excluded from the study were subjects with myocardial infarction, stroke or hospitalisation for heart failure in the period of 2 months prior to enrolment, or heart failure of NYHA classes III or IV.

A total of 1,428 subjects were enrolled in the study and randomised to the 4 treatment arms *(approx. 239 subjects per tirzepatide arm + insulin glargine ± metformin versus 711 subjects in the comparator arm with insulin glargine + insulin lispro ± metformin)*.

Relevant sub-population for patient group d1

Relevant for the assessment of the patient population d1 is the percentage of study participants who had no manifest cardiovascular disease at the start of study. This was 82% of the total study population. Accordingly, 584 subjects received the basal insulin with tirzepatide *(5 mg, 10 mg or 15 mg)*, while 587 subjects in the comparator arm were treated with insulin glargine and insulin lispro.

Treatment phase and target value-based titration based on fasting blood glucose values

An insulin optimisation phase took place up to 10 weeks before randomisation. Participants whose insulin regimen did not consist of insulin glargine had to be switched to insulin glargine *(U100)* . At the same time, the oral antidiabetic therapy administered during pretreatment had to be discontinued, with the exception of metformin.

At the start of study treatment, the dose of insulin glargine was reduced by 30% in all randomised patients in order to reduce the risk of hypoglycaemia. Insulin glargine and insulin

lispro were then titrated according to a predefined schedule. A fasting blood glucose target value of 100 to 125 mg/dl was targeted for all study participants.

As in the SURPASS-4 study described above, no predefined patient-individual treatment goals were agreed in the SURPASS-6 study, although this is recommended in the guidelines (see above). Treatment with the different doses of tirzepatide was also randomised, as in the SURPASS-4 study. It was not checked in advance which subjects in the intervention arms undoubtedly needed higher doses of tirzepatide. Despite these uncertainties, the data from sub-population d1 of the SURPASS-6 study are used for the early benefit assessment.

Extent and probability of the additional benefit – SURPASS-6, patient population d1

Mortality

No statistically significant differences were detected between the treatment arms regarding overall mortality.

Morbidity

Diabetic retinopathies

For the endpoint "diabetic retinopathies", no statistically significant difference was detected between the treatment arms.

Health status (EQ-5D VAS)

Health status was assessed in the study using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the improvement by ≥ 15 points at week 52, there was a statistically significant difference between the treatment arms in favour of tirzepatide.

Myocardial infarction

For the endpoint of myocardial infarction, 4 events occurred in the comparator arm. It is not possible to estimate the effect.

Hospitalisation due to angina pectoris or heart failure

For the endpoints "hospitalisation due to angina pectoris or heart failure" , 1 event occurred in the comparator arm in each case. It is not possible to estimate the effect.

Cerebrovascular morbidity

For the endpoint "cerebrovascular morbidity", no statistically significant differences were detected between the treatment arms.

Additionally presented endpoints

HbA1c change

There was a statistically significant difference in the change in the HbA1c value from the start of study up to week 52 to the advantage of tirzepatide. The endpoint "HbA1c" is a surrogate parameter and not patient-relevant per se.

Body weight and BMI

The change in body weight and BMI each showed a statistically significant difference to the advantage of tirzepatide. The endpoints body weight and BMI are surrogate parameters and not patient-relevant per se.

Quality of life

Short Form-36 Health Survey Version 2

Health-related quality of life endpoint was collected in the SURPASS-6 study using the Short Form-36 Health Survey version 2 (SF-36v2).

SF-36 is a generic instrument for measuring health-related quality of life, consisting of 8 domains and a total of 36 questions. In the assessment, the physical composite summary (PCS) scale and the mental component summary (MCS) scale of the generic quality of life questionnaire SF-36v2 were each used for the improvement by 15% of the scale range at week 52. This corresponds to a change of ≥ 9.7 points for the PCS and ≥ 9.6 points for the MCS.

For the physical component summary (PCS) score of the SF-36v2, there is no statistically significant difference between the treatment arms.

For the mental composite summary (MCS) score of the SF-36v2, there was a statistically significant difference in favour of tirzepatide compared to the comparator arm.

Side effects

In the side effects endpoint category, results are available for the overall rate of serious adverse events, discontinuation due to adverse events, and data on specific adverse events.

Overall rates

Serious adverse events (SAE)

For the endpoint of SAEs, there was a statistically significant advantage in favour of tirzepatide compared to the comparator arm.

Discontinuation due to adverse events (AEs)

For the endpoint of discontinuation due to AEs, there is a disadvantage of tirzepatide over the comparator arm.

Specific AEs

Pancreatitis

None of the subjects in the relevant sub-population experienced pancreatitis during the study.

Non-severe symptomatic, confirmed hypoglycaemia

For the endpoint "non-severe symptomatic, confirmed hypoglycaemia", results are available for both the plasma glucose limit value of ≤ 54 mg/dl and < 70 mg/dl *(the latter is presented additionally)*.

For both operationalisations, there was a statistically significant advantage of tirzepatide over the comparator arm.

Severe hypoglycaemia

In the SURPASS-6 study, severe hypoglycaemia was collected via the SAE. For this endpoint, there was a statistically significant advantage of tirzepatide over the comparator arm.

Gastrointestinal disorders

For the endpoint "*gastrointestinal disorders*" (SOC), here for PT nausea, vomiting and diarrhoea, there was a statistically significant disadvantage of tirzepatide over the comparator arm.

Overall assessment

For the assessment of patient population d1, data from a sub-population of the SURPASS-6 study of adults with type 2 diabetes mellitus without manifest cardiovascular disease are available. The study compared the treatment of tirzepatide versus insulin lispro, in each case in combination with insulin glargine with or without metformin in insulin-experienced adults. The treatment duration was 52 weeks. The insulin regimen in the comparator arm corresponds to intensified insulin therapy (ICT) according to the appropriate comparator therapy.

Data are available on different endpoints from the endpoint categories of mortality, morbidity, health-related quality of life and side effects.

For the endpoints collected, there were statistically significant differences between the treatment arms to the advantage of tirzepatide in morbidity, health status (EQ-5D VAS), quality of life for the SF-36 endpoint in the mental component summary score and for side effects in the overall rates of SAEs. At the same time, there were statistically significant disadvantages of tirzepatide compared to the comparator arm with regard to side effects in the endpoint of discontinuation due to AEs. In detail, the specific AEs also show advantages in the avoidance of both severe hypoglycaemia and non-severe symptomatic, confirmed hypoglycaemia and a disadvantage in gastrointestinal disorders (nausea, vomiting, diarrhoea).

No statistically significant differences were found between the treatment arms for the other endpoints, including quality of life in the physical component summary score of the SF-36.

Overall, there were minor positive effects for tirzepatide compared with the appropriate comparator therapy. The extent of the additional benefit is therefore classified as minor.

Reliability of data (probability of additional benefit)

In the SURPASS-6 study, an open-label comparison was made between tirzepatide + insulin glargine ± metformin and insulin glargine + insulin lispro ± metformin. Due to the open-label study design, there are limitations that minimise the significance of the results. Furthermore, the study has methodological limitations. These include the lack of patient-individual predefined treatment goals and uncertainties with regard to treatment with tirzepatide in accordance with the product information, who were randomised to the arms at higher doses of tirzepatide.

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

Patient group d2)

Data from the SURPASS-6 study were provided to assess the additional benefit of tirzepatide for the treatment of adults with type 2 diabetes mellitus and manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current insulin regimen.

SURPASS-6 study

For a general description of the study design with regard to the patients enrolled and the treatment with the trial medication, please refer to the above-mentioned explanations under patient group d1 .

Relevant sub-population for patient group d2

The relevant sub-population for the assessment of patient group d2 comprises adults with type 2 diabetes mellitus and manifest cardiovascular disease, which accounted for 18% of the total study population. This corresponded to 133 subjects receiving tirzepatide treatment versus 124 subjects receiving intensified insulin therapy with insulin glargine and insulin lispro.

No guideline-compliant treatment of manifest cardiovascular disease

According to the inclusion criteria, only subjects who had received a combination therapy of basal insulin with only metformin, sulphonyl ureas or DPP-4 inhibitors as prior therapy in the 90 days prior to randomisation could be enrolled in the study. Accordingly, no patients were eligible for enrolment in the study if they were also receiving treatment with SGLT-2 inhibitors or GLP-1-RA as part of their previous insulin regimen. In addition, SGLT-2 inhibitors and GLP-1-RA were generally not permitted during the treatment phase. This approach contradicts the guideline recommendations, which explicitly specify the combination of basal insulin and metformin together with an SGLT-2 inhibitor or a GLP-1-RA for antidiabetic treatment in the presence of manifest cardiovascular disease. The appropriate comparator therapy also includes the intake of empagliflozin, dapagliflozin or liraglutide by adults with manifest cardiovascular disease who receive basal oral therapy (BOT) as an insulin regimen. Positive effects in the prevention of deaths and cardiovascular events have been demonstrated for these active ingredients.

For a correct implementation of the appropriate comparator therapy for the relevant sub-population, further optimisation of basal insulin by further combination with the above-mentioned active ingredients with a positive effect on cardiovascular events would have been necessary. The NVL[2] also recommends continuing the combination therapy of metformin and an SGLT-2 inhibitor or a GLP-1-RA as part of the escalation of insulin therapy when intensifying from a basal insulin to a mixed insulin or an intensified insulin therapy (ICT).

The fact that in the SURPASS-6 study there was an immediate escalation to ICT without prior optimisation by adding empagliflozin, dapagliflozin or liraglutide is generally viewed critically due to the inappropriate treatment of cardiovascular disease and the associated high risk of hypoglycaemia.

Overall, the SURPASS-6 study is therefore unsuitable for the early benefit assessment of patient group d2. An additional benefit is not proven.

2.1.4 Summary of the assessment

This is the early benefit assessment of the new active ingredient Mounjaro with the active ingredient tirzepatide for the treatment of adults with inadequately controlled type 2 diabetes mellitus.

In the therapeutic indication under consideration, 4 patient populations are included, each with two sub-populations.

Patient group a1)

For insulin-naïve adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous medicinal therapy consisting of one hypoglycaemic agent, in addition to diet and exercise, the following was determined by the G-BA as an appropriate comparator therapy:
Patient-individual therapy, taking into account the patient-individual therapeutic goal, depending on comorbidities, diabetes duration, any risks of hypoglycaemia, under selection of:

- metformin + sulphonylureas (glibenclamide or glimepiride),
- metformin + sitagliptin,
- metformin + empagliflozin,
- metformin + liraglutide.

No studies were presented versus the appropriate comparator therapy. An additional benefit is not proven.

Patient group a2)

For insulin-naïve adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous medicinal therapy consisting of one hypoglycaemic agent, in addition to diet and exercise, the following was determined by the G-BA as an appropriate comparator therapy:

- metformin + empagliflozin, or
- metformin + liraglutide, or
- metformin + dapagliflozin.

No studies were presented versus the appropriate comparator therapy. An additional benefit is not proven.

Patient group b1)

For insulin-naïve adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous medicinal therapy consisting of two hypoglycaemic agents, in addition to diet and exercise, and for whom there is no indication for insulin therapy, the following was determined by the G-BA as the appropriate comparator therapy:

- metformin + empagliflozin + sitagliptin, or
- metformin + empagliflozin + liraglutide.

No data were presented versus the appropriate comparator therapy. An additional benefit is not proven.

Patient group b2)

For insulin-naïve adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous medicinal therapy consisting of two hypoglycaemic agents, in addition to diet and exercise, and for whom there is no indication for insulin therapy, the following was determined by the G-BA as an appropriate comparator therapy:

- metformin + empagliflozin + liraglutide, or
- metformin + dapagliflozin + liraglutide.

No data were presented versus the appropriate comparator therapy. An additional benefit is not proven.

Patient group c1)

For insulin-naïve adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least two blood glucose-lowering drugs in addition to diet and exercise, and for whom there is an indication for insulin therapy, the following was determined by the G-BA as the appropriate comparator therapy:

- human insulin + metformin.

No data were presented versus the appropriate comparator therapy. An additional benefit is not proven.

Patient group c2)

For insulin-naïve adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous medicinal therapy consisting of at least two hypoglycaemic agents, in addition to diet and exercise, and for whom there is an indication for insulin therapy, the following was determined by the G-BA as the appropriate comparator therapy:

- human insulin + metformin+ empagliflozin, or
- human insulin + metformin + dapagliflozin, or
- human insulin + metformin + liraglutide.

A sub-population of patients with manifest cardiovascular disease from the SURPASS-4 study was presented. The study compared the treatment of tirzepatide versus insulin glargine, each with metformin and an SGLT-2 inhibitor for 52 weeks.

The SURPASS-4 study has methodological uncertainties. Due to different treatment goals between the treatment groups with a strict insulin titration to a fasting blood glucose value of < 100 mg/dl, which was specified exclusively in the comparator arm, there is no fair comparison between the intervention and control arm overall. Based on the SURPASS-4 study, it is therefore not possible to draw any conclusions about the additional benefit. An additional benefit is not proven.

Patient group d1)

For insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous insulin regimen, in addition to diet and exercise, the following was determined by the G-BA to be an appropriate comparator therapy:

- escalation of insulin therapy (conventional therapy (CT) if necessary + metformin or dulaglutide or intensified insulin therapy (ICT)).

A sub-population of patients without manifest cardiovascular disease from the SURPASS-6 study was presented. The treatment of tirzepatide versus insulin lispro was compared in each case with insulin glargine with or without metformin for 52 weeks.

Tirzepatide showed statistically significant advantages over the comparator arm in morbidity in health status (EQ5D-VAS), in quality of life in the SF-36 mental component summary score endpoint and in side effects in the overall rate of SAEs as well as in the prevention of severe hypoglycaemia and non-severe symptomatic confirmed hypoglycaemia. At the same time, there were statistically significant disadvantages of tirzepatide over the comparator arm in

terms of side effects for the endpoint of discontinuation due to AEs and gastrointestinal disorders (nausea, vomiting, diarrhoea). For the remaining endpoints, there were no statistically significant differences between the treatment arms.

Overall, a hint for a minor additional benefit compared with the appropriate comparator therapy is identified for tirzepatide in the patient group d1.

Patient group d2)

For insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their previous insulin regimen, in addition to diet and exercise, was determined by the G-BA to be an appropriate comparator therapy:

- Escalation of insulin therapy: conventional therapy (CT) or intensified insulin therapy (ICT), in each case in combination with metformin and empagliflozin or dapagliflozin or liraglutide.

A sub-population of patients with manifest cardiovascular disease from the SURPASS-6 study was presented. The treatment of tirzepatide versus insulin lispro was compared in each case with insulin glargine with or without metformin for 52 weeks.

According to the inclusion criteria, no subjects were eligible for the study who were also receiving therapy with SGLT-2 inhibitors or GLP-1-RA as part of their previous insulin regimen. In addition, SGLT-2 inhibitors and GLP-1-RA were generally not permitted during the treatment phase. This approach contradicts the guideline recommendations regarding the treatment of adults with type 2 diabetes and manifest cardiovascular disease. According to the appropriate comparator therapy, it is also expected that this patient population will receive treatment with empagliflozin, dapagliflozin or liraglutide. Based on the SURPASS-6 study, no statements on the additional benefit can therefore be derived for patient group d2. An additional benefit 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 (SHI).

The resolution is based on the patient numbers stated in the dossier of the pharmaceutical company, based on the information in the previous resolution in this therapeutic indication.

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 Mounjaro (active ingredient: tirzepatide) at the following publicly accessible link (last access: 21 March 2024):

https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf

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

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

Treatment duration and consumption

With regard to consumption, the average annual 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-individual.

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

For tirzepatide, the starting dose is 2.5 mg once daily. If additional lowering of glucose lowering is necessary, the dose can be increased to 5 mg once daily. The recommended maintenance dose is 5 mg, 10 mg or 15 mg according to the product information.

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 potency of 1,000 mg metformin/tablet is used as the basis for the cost representation.

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 potency of 3.5 mg, as this dosage covers all the dosages recommended in the product information.

Therapy with glimepiride in combination with other oral anti-diabetic 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.

The recommended dose of sitagliptin is 100 mg once daily.

The starting 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).

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 potencies are taken into account for the cost representation.

The recommended dose of dapagliflozin is 10 mg once daily.

For dulaglutide, as part of combination therapy with other medicines, a dose of 1.5 mg once weekly is recommended, which can be increased to a maximum dose of 4.5 mg once weekly.

A variety of different insulin dosing regimens are available for insulin therapy. In addition, according to the insulin dosing scheme 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[8], 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 bodyweight of 77.7 kg is assumed for the bodyweight according to the official representative statistics "Microcensus 2021"[9].

Consequently, weight differences between women and men as well as the fact that the bodyweight of patients with type 2 diabetes mellitus may be higher than the average value of 77.7 kg are not taken into account for the cost calculation.

[8] Product information for Insuman® Basal, last revised: July 2020.
[9] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Treatment period:

a1) **Insulin-naïve** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tirzepatide	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed[10]:				
Metformin	Continuously, 2-3 x daily	365	1	365
Glibenclamide	Continuously, 1-2 x daily	365	1	365
Glimepiride	Continuously, 1 x daily	365	1	365
Sitagliptin	Continuously, 1 x daily	365	1	365
Empagliflozin	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Metformin	Continuously, 2-3 x daily	365	1	365
Glibenclamide or	Continuously, 1-2 x daily	365	1	365
Glimepiride	Continuously, 1 x daily	365	1	365
Sitagliptin	Continuously, 1 x daily	365	1	365
Empagliflozin	Continuously, 1 x daily	365	1	365
Liraglutide	Continuously, 1 x daily	365	1	365

[10] As an example of the combination of tirzepatide with a hypoglycaemic agent, metformin, glibenclamide, glimepiride, sitagliptin and empagliflozin are presented as possible concomitant active ingredients

a2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tirzepatide	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed[11]:				
Metformin	Continuously, 2-3 x daily	365	1	365
Empagliflozin	Continuously, 1 x daily	365	1	365
Dapagliflozin	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Metformin	Continuously, 2-3 x daily	365	1	365
Empagliflozin	Continuously, 1 x daily	365	1	365
Liraglutide	Continuously, 1 x daily	365	1	365
Dapagliflozin	Continuously, 1 x daily	365	1	365

[11] Metformin, empagliflozin, and dapagliflozin are presented as possible concomitant active ingredients, exemplifying the combination of tirzepatide with a hypoglycemic agent.

b1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tirzepatide	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed[12]:				
Metformin	Continuously, 2-3 x daily	365	1	365
Sitagliptin	Continuously, 1 x daily	365	1	365
Empagliflozin	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Metformin	Continuously, 2-3 x daily	365	1	365
Sitagliptin	Continuously, 1 x daily	365	1	365
Empagliflozin	Continuously, 1 x daily	365	1	365
Liraglutide	Continuously, 1 x daily	365	1	365

[12] Metformin, sitagliptin, and empagliflozin are presented as possible concomitant active ingredients, exemplifying the combination of tirzepatide with two hypoglycemic agents.

b2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tirzepatide	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed[13]:				
Metformin	Continuously, 2-3 x daily	365	1	365
Empagliflozin	Continuously, 1 x daily	365	1	365
Dapagliflozin	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Metformin	Continuously, 2-3 x daily	365	1	365
Empagliflozin	Continuously, 1 x daily	365	1	365
Liraglutide	Continuously, 1 x daily	365	1	365
Dapagliflozin	Continuously, 1 x daily	365	1	365

[13] Metformin and empagliflozin or metformin and dapagliflozin are presented as examples of possible concomitant active ingredients in the combination of tirzepatide with two hypoglycemic agents.

c1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is an indication for an insulin therapy**.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tirzepatide	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed[14]:				
Metformin	Continuously, 2-3 x daily	365	1	365
Human insulin (NPH-insulin)	Continuously, 1-2 x daily	365	1	365
Appropriate comparator therapy				
Metformin	Continuously, 2-3 x daily	365	1	365
Human insulin (NPH-insulin)	Continuously, 1-2 x daily	365	1	365

[14] As an example for the use in diabetics with a first-time indication for insulin therapy, the combination of tirzepatide with human insulin (NPH insulin) with and without metformin in the context of basal supported oral therapy (BOT) is shown.

c2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom there is an **indication for insulin therapy**.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tirzepatide	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed[15]:				
Metformin	Continuously, 2-3 x daily	365	1	365
Human insulin (NPH-insulin)	Continuously, 1-2 x daily	365	1	365
Appropriate comparator therapy				
Metformin	Continuously, 2-3 x daily	365	1	365
Empagliflozin	Continuously, 1 x daily	365	1	365
Liraglutide	Continuously, 1 x daily	365	1	365
Dapagliflozin	Continuously, 1 x daily	365	1	365
Human insulin (NPH-insulin)	Continuously, 1-2 x daily	365	1	365

[15] The combination of tirzepatide with human insulin (NPH insulin) and with metformin in the context of basal supported oral therapy (BOT) is shown as an example for the use in type 2 diabetics with a first-time indication for insulin therapy.

d1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tirzepatide	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed[16]:				
Metformin	Continuously, 2-3 x daily	365	1	365
Conventional insulin therapy (CT) mixed insulin	Continuously, 1-2 x daily	365	1	365
Appropriate comparator therapy				
Metformin	Continuously, 2-3 x daily	365	1	365
Dulaglutide	Continuously, 1 x every 7 days	52.1	1	52.1
Conventional insulin therapy (CT) mixed insulin	Continuously, 1-2 x daily	365	1	365
Intensified insulin therapy (ICT) Human insulin (NPH-insulin) Human insulin (bolus insulin)	 Continuously, 1-2 x daily Continuously, 3 x daily	 365 365	 1 1	 365 365

[16] The combination with mixed insulin is shown as an example of the combination of tirzepatide with insulin in the context of escalation of insulin therapy, in this case with conventional insulin therapy.

d2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tirzepatide	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed[17]:				
Metformin	Continuously, 2-3 x daily	365	1	365
Conventional insulin therapy (CT) Mixed insulin	Continuously, 1-2 x daily	365	1	365
Appropriate comparator therapy				
Metformin	Continuously, 2-3 x daily	365	1	365
Empagliflozin	Continuously, 1 x daily	365	1	365
Liraglutide	Continuously, 1 x daily	365	1	365
Dapagliflozin	Continuously, 1 x daily	365	1	365
Conventional insulin therapy (CT) mixed insulin	Continuously, 1–2 x daily	365	1	365
Intensified insulin therapy (ICT) Human insulin (NPH-insulin)	Continuously, 1-2 x daily	365	1	365
Human insulin (bolus insulin)	Continuously, 3 x daily	365	1	365

[17] The combination with mixed insulin and metformin is shown as an example of the combination of tirzepatide with insulin in the context of escalation of insulin therapy, in this case with conventional insulin therapy.

Consumption:

a1) **Insulin-naïve** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control with their **current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

Designation of the therapy	Dosage/ application	Dosage/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tirzepatide	5 mg – 15 mg	5 mg – 15 mg	1 x 5 mg – 1 x 15 mg	52.1 52.1	52.1 x 5 mg – 52.1 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed:					
Metformin	500 mg - 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365 365	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
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	365 365	182.5 x 3.5 mg - 1095.0 x 3.5 mg
Glimepiride	1 mg - 6 mg	1 mg - 6 mg	1 x 1 mg - 1 x 6 mg	365.0 365.0	365.0 x 1 mg - 365.0 x 6 mg
Sitagliptin	100 mg	100 mg	1 x 100 mg	365.0	365.0 x 100 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365.0 365.0	365.0 x 10 mg - 365.0 x 25 mg
Appropriate comparator therapy					
Metformin	500 mg - 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
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	365.0 365.0	182.5 x 3.5 mg - 1095.0 x 3.5 mg
Glimepiride	1 mg - 6 mg	1 mg - 6 mg	1 x 1 mg - 1 x 6 mg	365.0 365.0	365.0 x 1 mg - 365.0 x 6 mg
Sitagliptin	100 mg	100 mg	1 x 100 mg	365.0	365.0 x 100 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365.0 365.0	365.0 x 10 mg - 365.0 x 25 mg
Liraglutide[18]	1.2 mg -	1.2 mg -	1 x 1.2 mg -	365.0	365.0 x 1.2 mg -

[18] According to the product information, each pre-filled pen contains 18 mg liraglutide in 3 ml solution, corresponding to 10 - 15 single doses. Packs of 2, 5 and 10 pre-filled pens are available.

Designation of the therapy	Dosage/ application	Dosage/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
	1.8 mg	1.8 mg	1 x 1.8 mg	365.0	365.0 x 1.8 mg

a2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of one hypoglycaemic agent**, in addition to diet and exercise

Designation of the therapy	Dosage/ application	Dosage/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tirzepatide	5 mg – 15 mg	5 mg – 15 mg	1 x 5 mg – 1 x 15 mg	52.1 52.1	52.1 x 5 mg – 52.1 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed:					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Empagliflozin	10 mg – 25 mg	10 mg – 25 mg	1 x 10 mg – 1 x 25 mg	365.0 365.0	365.0 x 10 mg – 365.0 x 25 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365.0 x 10 mg
Appropriate comparator therapy					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Empagliflozin	10 mg – 25 mg	10 mg – 25 mg	1 x 10 mg – 1 x 25 mg	365.0 365.0	365.0 x 10 mg - 365.0 x 25 mg
Liraglutide[18]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365.0 365.0	365.0 x 1.2 mg - 365.0 x 1.8 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365.0 x 10 mg

b1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Designation of the therapy	Dosage/ application	Dosage/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tirzepatide	5 mg – 15 mg	5 mg – 15 mg	1 x 5 mg – 1 x 15 mg	52.1 52.1	52.1 x 5 mg – 52.1 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed:					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Sitagliptin	100 mg	100 mg	1 x 100 mg	365.0	365.0 x 100 mg
Empagliflozin	10 mg – 25 mg	10 mg – 25 mg	1 x 10 mg – 1 x 25 mg	365.0 365.0	365.0 x 10 mg – 365.0 x 25 mg
Appropriate comparator therapy					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Sitagliptin	100 mg	100 mg	1 x 100 mg	365.0	365.0 x 100 mg
Empagliflozin	10 mg – 25 mg	10 mg – 25 mg	1 x 10 mg – 1 x 25 mg	365.0 365.0	365.0 x 10 mg – 365.0 x 25 mg
Liraglutide[1818]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365.0 365.0	365.0 x 1.2 mg - 365.0 x 1.8 mg

b2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is no indication for an insulin therapy**.

Designation of the therapy	Dosage/ application	Dosage/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tirzepatide	5 mg – 15 mg	5 mg – 15 mg	1 x 5 mg – 1 x 15 mg	52.1 52.1	52.1 x 5 mg – 52.1 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed:					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Empagliflozin	10 mg – 25 mg	10 mg – 25 mg	1 x 10 mg – 1 x 25 mg	365.0 365.0	365.0 x 10 mg – 365.0 x 25 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365.0 x 10 mg
Appropriate comparator therapy					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Empagliflozin	10 mg – 25 mg	10 mg – 25 mg	1 x 10 mg – 1 x 25 mg	365.0 365.0	365.0 x 10 mg – 365.0 x 25 mg
Liraglutide[188]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365.0 365.0	365.0 x 1.2 mg - 365.0 x 1.8 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365.0 x 10 mg

c1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is an indication for an insulin therapy**.

Designation of the therapy	Dosage/ application	Dosage/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tirzepatide	5 mg – 15 mg	5 mg – 15 mg	1 x 5 mg – 1 x 15 mg	52.1 52.1	52.1 x 5 mg – 52.1 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed:					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Human insulin (NPH-insulin)	0.5 - 1 I.U. / kg BW	38.85 - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365 365	14,180.25 I.U. - 28360.5 I.U.
Appropriate comparator therapy					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Human insulin (NPH-insulin)	0.5 - 1 I.U. / kg BW	38.85 - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365 365	14180.25 I.U. - 28360.5 I.U.

c2) **Insulin-naïve** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom there is an **indication for insulin therapy**.

Designation of the therapy	Dosage/ application	Dosage/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tirzepatide	5 mg – 15 mg	5 mg – 15 mg	1 x 5 mg – 1 x 15 mg	52.1 52.1	52.1 x 5 mg – 52.1 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed:					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Human insulin (NPH-insulin)	0.5 - 1 I.U. / kg BW	38.85 - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365 365	14180.25 I.U. - 28360.5 I.U.
Appropriate comparator therapy					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Empagliflozin	10 mg – 25 mg	10 mg – 25 mg	1 x 10 mg – 1 x 25 mg	365.0 365.0	365.0 x 10 mg – 365.0 x 25 mg
Liraglutide[18]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365.0 365.0	365.0 x 1.2 mg - 365.0 x 1.8 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365.0 x 10 mg
Human insulin (NPH-insulin)	0.5 - 1 I.U. / kg BW	38.85 - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365 365	14180.25 I.U. - 28360.5 I.U.

d1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Designation of the therapy	Dosage/ application	Dosage/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tirzepatide	5 mg – 15 mg	5 mg – 15 mg	1 x 5 mg – 1 x 15 mg	52.1 52.1	52.1 x 5 mg – 52.1 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed:					
Metformin	500 mg - 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Conventional insulin therapy (CT) Mixed insulin	0.5 I.U. - 1.0 I.U. / kg BW	38.85 I.U. - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365.0 365.0	14180.25 I.U. – 28360.5 I.U.
Appropriate comparator therapy					
Metformin	500 mg - 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Dulaglutide	1.5 mg - 4.5 mg	1.5 mg - 4.5 mg	1 x 1.5 mg - 1 x 4.5 mg	52.1 52.1	52.1 x 1.5 mg - 52.1 x 4.5 mg
Conventional insulin therapy (CT) Mixed insulin	0.5 I.U. - 1.0 I.U. / kg BW	38.85 I.U. - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365.0 365.0	14,180.25 I.U. – 28,360.5 I.U.
Intensified insulin therapy (ICT) Human insulin (NPH-insulin) Human insulin (Bolus insulin)	0.2 - 0.6 I.U. / kg BW 0.2 - 0.6 I.U. / kg BW	15.54 - 46.62 I.U. 15.54 - 46.62 I.U.	1 x 15.54 I.U. - 1 x 46.62 I.U. 1 x 15.54 I.U. - 1 x 46.62 I.U.	365 365 365 365	5,672.1 I.U. - 17,016.3 I.U. 5,672.1 I.U. - 17,016.3 I.U.

d2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their previous insulin regime**, in addition to diet and exercise

Designation of the therapy	Dosage/ application	Dosage/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tirzepatide	5 mg – 15 mg	5 mg – 15 mg	1 x 5 mg – 1 x 15 mg	52.1 52.1	52.1 x 5 mg – 52.1 x 15 mg
Concomitant active ingredient of the medicinal product to be assessed:					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Conventional insulin therapy (CT) Mixed insulin	0.5 I.U. - 1.0 I.U. / kg BW	38.85 I.U. - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365.0 365.0	14,180.25 I.U. – 28,360.5 I.U.
Appropriate comparator therapy					
Metformin	500 mg – 1,000 mg	1,000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0 365.0	365.0 x 1,000 mg - 1,095.0 x 1,000 mg
Empagliflozin	10 mg – 25 mg	10 mg – 25 mg	1 x 10 mg – 1 x 25 mg	365.0 365.0	365.0 x 10 mg – 365.0 x 25 mg
Liraglutide[18]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365.0 365.0	365.0 x 1.2 mg - 365.0 x 1.8 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365.0 x 10 mg
Conventional insulin therapy (CT) Mixed insulin	0.5 I.U. - 1.0 I.U. / kg BW	38.85 I.U. - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365.0 365.0	14,180.25 I.U. – 28,360.5 I.U.
Intensified insulin therapy (ICT) Human insulin (NPH-insulin)	0.2 - 0.6 I.U. / kg BW	15.54 - 46.62 I.U.	1 x 15.54 I.U. - 1 x 46.62 I.U.	365 365	5,672.1 I.U. - 17,016.3 I.U.
Human insulin (Bolus insulin)	0.2 - 0.6 I.U. / kg BW	15.54 - 46.62 I.U.	1 x 15.54 I.U. - 1 x 46.62 I.U.	365 365	5,672.1 I.U. - 17,016.3 I.U.

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

The fixed reimbursement rate was used as the basis for calculating the treatment costs for the active ingredients 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.

Costs of the medicinal products:

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					
Tirzepatide 5 mg	4 SFI	€ 259.48	€ 2.00	€ 13.74	€ 234.74
Tirzepatide 15 mg	4 SFI	€ 345.50	€ 2.00	€ 18.50	€ 325.00
If necessary + dapagliflozin 10 mg	98 FCT	€ 239.30	€ 2.00	€ 0.00	€ 237.30
if necessary + empagliflozin 10 mg	100 FCT	€ 244.39	€ 2.00	€ 12.90	€ 229.49
if necessary + empagliflozin 25 mg	100 FCT	€ 192.67	€ 2.00	€ 10.04	€ 180.63
if necessary + glibenclamide 3.5 mg[19]	180 TAB	€ 15.27	€ 2.00	€ 0.31	€ 12.96
If necessary + glimepiride 1 mg[19]	180 TAB	€ 17.21	€ 2.00	€ 0.47	€ 14.74
If necessary + glimepiride 6 mg[19]	180 TAB	€ 82.86	€ 2.00	€ 5.66	€ 75.20
If necessary + metformin 1,000 mg[19]	180 FCT	€ 19.11	€ 2.00	€ 0.62	€ 16.49
If necessary + sitagliptin 100 mg	98 FCT	€ 29.10	€ 2.00	€ 0.84	€ 26.26
If necessary + human insulin (NPH insulin)[19]	3,000 I.U.	€ 89.98	€ 2.00	€ 6.22	€ 81.76
If necessary + conventional insulin therapy (CT) Mixed insulin[19]	3,000 I.U.	€ 89.98	€ 2.00	€ 6.22	€ 81.76
Appropriate comparator therapy					
Dapagliflozin 10 mg	98 FCT	€ 239.30	€ 2.00	€ 0.00	€ 237.30

[19] Fixed reimbursement rate

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
Dulaglutide 1.5 mg	12 SFI	€ 287.75	€ 2.00	€ 15.30	€ 270.45
Dulaglutide 4.5 mg	12 SFI	€ 287.75	€ 2.00	€ 15.30	€ 270.45
Empagliflozin 10 mg	100 FCT	€ 244.39	€ 2.00	€ 12.90	€ 229.49
Empagliflozin 25 mg	100 FCT	€ 192.67	€ 2.00	€ 10.04	€ 180.63
Glibenclamide 3.5 mg[19]	180 TAB	€ 15.27	€ 2.00	€ 0.31	€ 12.96
Glimepiride 1 mg[19]	180 TAB	€ 17.21	€ 2.00	€ 0.47	€ 14.74
Glimepiride 6 mg[19]	180 TAB	€ 82.86	€ 2.00	€ 5.66	€ 75.20
Liraglutide 18 mg	100 – 150 SD	€ 660.82	€ 2.00	€ 35.96	€ 622.86
Metformin 1,000 mg[19]	180 FCT	€ 19.11	€ 2.00	€ 0.62	€ 16.49
Sitagliptin 100 mg	98 FCT	€ 29.10	€ 2.00	€ 0.84	€ 26.26
Human insulin (NPH insulin)[19]	3,000 I.U.	€ 89.98	€ 2.00	€ 6.22	€ 81.76
Mixed insulin[19]	3,000 I.U.	€ 89.98	€ 2.00	€ 6.22	€ 81.76
Human insulin (bolus insulin)[19]	3,000 I.U.	€ 89.98	€ 2.00	€ 6.22	€ 81.76
Abbreviations: SD = single doses; FCT = film-coated tablets, I.U. = International Units; SFI = solution for injection; TAB = tablets					

LAUER-TAXE® last revised: 15 April 2024

Costs for additionally required SHI services:

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

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Costs for additionally required SHI services:

Designation of the therapy	Designation	Cost/ pack[20]	Number	Consumption/ year
Concomitant active ingredient of the medicinal product to be assessed				
Human insulin (NPH insulin)	Blood glucose test strips	€ 15.95	1-3 x daily	365.0 – 1095.0
	Lancets	€ 4.20	1 – 3 x daily	365.0 – 1,095.0
	Disposable needles	€ 13.00	1 - 2 x daily	365.0 – 730.0
Conventional insulin therapy (CT, mixed insulin)	Blood glucose test strips	€ 15.95	1-3 x daily	365.0 – 1,095.0
	Lancets	€ 4.20	1 – 3 x daily	365.0 – 1,095.0
	Disposable needles	€ 13.00	1 - 2 x daily	365.0 – 730.0
Designation of the therapy	Designation	Cost/ pack[20]	Number	Consumption/ year
Appropriate comparator therapy				
Human insulin (NPH insulin)	Blood glucose test strips	€ 15.95	1-3 x daily	365.0 – 1,095.0
	Lancets	€ 4.20	1 – 3 x daily	365.0 – 1,095.0
	Disposable needles	€ 13.00	1 - 2 x daily	365.0 – 730.0
Conventional insulin therapy (CT, mixed insulin)	Blood glucose test strips	€ 15.95	1-3 x daily	365.0 – 1,095.0
	Lancets	€ 4.20	1 – 3 x daily	365.0 – 1,095.0
	Disposable needles	€ 13.00	1 - 2 x daily	365.0 – 730.0
Intensified conventional insulin therapy	Blood glucose test strips	€ 15.95	4 – 6 x daily	1,460 – 2,190
	Lancets	€ 4.20	4 – 6 x daily	1,460 – 2,190
	Disposable needles	€ 13	4 – 5 x daily	1,460 – 1,825
Liraglutide	Disposable needles	€ 13	1 x daily	365

[20] 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®, last revised: 15 April 2024.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1

SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a1) Insulin-naïve adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current medicinal therapy consisting of one hypoglycaemic agent, in addition to diet and exercise

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. This therapeutic indication is a combination in addition to other medicinal products for the treatment for diabetes mellitus according to the requirements in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:
Product information for tirzepatide (Mounjaro); Mounjaro®; last revised: December 2023

a2) Insulin-naïve adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current medicinal therapy consisting of one hypoglycaemic agent, in addition to diet and exercise

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. This therapeutic indication is a combination in addition to other medicinal products for the treatment for diabetes mellitus according to the requirements in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:
Product information for tirzepatide (Mounjaro); Mounjaro®; last revised: December 2023

b1) Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current medicinal therapy consisting of two hypoglycaemic agents, in addition to diet and exercise, and for whom there is no indication for an insulin therapy.

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal

product. This therapeutic indication is a combination in addition to other medicinal products for the treatment for diabetes mellitus according to the requirements in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:
Product information for tirzepatide (Mounjaro); Mounjaro®; last revised: December 2023

b2) Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current medicinal therapy consisting of two hypoglycaemic agents, in addition to diet and exercise, and for whom there is no indication for an insulin therapy.

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. This therapeutic indication is a combination in addition to other medicinal products for the treatment for diabetes mellitus according to the requirements in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:
Product information for tirzepatide (Mounjaro); Mounjaro®; last revised: December 2023

c1) Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current medicinal therapy consisting of at least two hypoglycaemic agents, in addition to diet and exercise, and for whom there is an indication for an insulin therapy.

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. This therapeutic indication is a combination in addition to other medicinal products for the treatment for diabetes mellitus according to the requirements in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:
Product information for tirzepatide (Mounjaro); Mounjaro®; last revised: December 2023

c2) Insulin-naïve adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current medicinal therapy consisting of at least two hypoglycaemic agents, in addition to diet and exercise, and for whom there is an indication for insulin therapy.

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. This therapeutic indication is a combination in addition to other medicinal products for the treatment for diabetes mellitus according to the requirements in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:
Product information for tirzepatide (Mounjaro); Mounjaro®; last revised: December 2023

d1) Insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease and who have not achieved adequate glycaemic control with their previous insulin regime, in addition to diet and exercise

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. This therapeutic indication is a combination in addition to other medicinal products for the treatment for diabetes mellitus according to the requirements in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:
Product information for tirzepatide (Mounjaro); Mounjaro®; last revised: December 2023

d2) Insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease and who have not achieved adequate glycaemic control with their previous insulin regime, in addition to diet and exercise

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. This therapeutic indication is a combination in addition to other medicinal products for the treatment for diabetes mellitus according to the requirements in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product

information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:
Product information for tirzepatide (Mounjaro); Mounjaro®; last revised: December 2023

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

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

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 25 January 2022.

On 13 November 2023, the pharmaceutical company submitted a dossier for the benefit assessment of tirzepatide to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 14 November 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 tirzepatide.

The dossier assessment by the IQWiG was submitted to the G-BA on 7 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 February 2024. The deadline for submitting statements was 7 March 2024.

The oral hearing was held on 25 March 2024.

By letter dated 26 March 2024, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 15 April 2024.

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 was discussed at the session of the subcommittee on 23 April 2024, and the proposed resolution was approved.

At its session on 2 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 January 2020	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	25 January 2022	New implementation of the appropriate comparator therapy
Working group Section 35a	19 March 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	25 March 2024	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	3 April 2024 16 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	23 April 2024	Concluding discussion of the draft resolution
Plenum	2 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 2 May 2024

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

Prof. Hecken