Tirzepatide
(type 2 diabetes mellitus)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 7 of the dossier assessment *Tirzepatid (Diabetes Mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by two persons.

IQWiG thanks the respondents and the Deutsche Diabetes Föderation e. V. (German Diabetes Federation) for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents and the Deutsche Diabetes Föderation e. V. were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BMI	body mass index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NYHA	New York Heart Association [NYHA]
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SGLT2	sodium-glucose cotransporter 2
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tirzepatide. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 14 November 2023.

Research question

The aim of this report is to assess the added benefit of tirzepatide as an adjunct to diet and exercise in adult patients with inadequately controlled type 2 diabetes mellitus in comparison with the appropriate comparator therapy (ACT)

- as monotherapy if the use of metformin is not indicated due to intolerances or contraindications
- as add-on therapy to other diabetes mellitus drugs.

The research questions shown in Table 2 result from the ACT specified by the G-BA. The G-BA created no separate research question for tirzepatide as monotherapy based on the assumption that, compared to the total population, only a small percentage of patients with type 2 diabetes mellitus are contraindicated for metformin.

Table 2: Research questions of the benefit assessment of tirzepatide (multipage table)

Research question	Therapeutic indication[a]	ACT[b]
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	Individualized therapy taking into account the treatment goal determined for the individual patient based on comorbidities, time since diabetes diagnosis, and potential risk factors for hypoglycaemia, selecting from: ▪ metformin + sulphonylurea (glibenclamide or glimepiride)[c], ▪ metformin + sitagliptin, ▪ metformin + empagliflozin, ▪ metformin + liraglutide
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	▪ Metformin + empagliflozin or ▪ metformin + liraglutide or ▪ metformin + dapagliflozin

Table 2: Research questions of the benefit assessment of tirzepatide (multipage table)

Research question	**Therapeutic indication**[a]	**ACT**[b]
3	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + sitagliptin or ▪ metformin + empagliflozin + liraglutide
4	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved sufficient glycaemic control with their ongoing drug treatment consisting of 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + liraglutide or ▪ metformin + dapagliflozin + liraglutide
5	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin[d] + metformin
6	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin[d] + metformin + empagliflozin or ▪ human insulin[d] + metformin + dapagliflozin or ▪ human insulin[d] + metformin + liraglutide
7	Insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (conventional therapy [CT], possibly + metformin or dulaglutide or intensified insulin therapy [ICT])[d]x

Table 2: Research questions of the benefit assessment of tirzepatide (multipage table)

Research question	Therapeutic indication[a]	ACT[b]
8	Insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (CT), possibly + metformin or empagliflozin or liraglutide or dapagliflozin or [ICT])[d]

a. Subdivision of the therapeutic indication according to the G-BA.

- It is assumed that pharmacotherapy is initiated only after failure of basic treatment alone (non-drug measures such as diet, exercise, etc.) and is always carried out in combination with said treatment.
- All guidelines relevant in the therapeutic indication cite drug therapy with metformin as the standard of care for patients with type 2 diabetes mellitus.
- Initial diabetes treatment is assumed to be metformin monotherapy.
- In case of inadequate glycaemic control under metformin monotherapy, guidelines recommend continuing metformin administration and intensifying treatment by adding another drug. Treatment regimens without metformin therefore require an explanation as to why metformin was contraindicated for the patient.
- As per the current metformin dosing recommendations, metformin is an option for an expanded patient population, including patients with moderate renal impairment (GFR ≥ 30 mL/min). Because compared to the total population, only a small percentage of patients with type 2 diabetes mellitus are contraindicated for metformin, patients with metformin contraindication were not designated as a separate group.
- Based on the results of cardiovascular outcome studies and the recommendations of the guideline, which show that the most robust data were shown in diabetic patients with existing cardiovascular disease, a distinction is made between patients with and without manifest cardiovascular disease when determining the ACT. The operationalization of the definition of patients with manifest cardiovascular disease should be based on criteria that are generally accepted and established in medical science.
- For the treatment of comorbidities in patients with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, coronary artery disease, etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be administered, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular disease characteristics of type 2 diabetes mellitus. For the treatment of comorbidities in patients with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, CHD, etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be administered, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular disease characteristics of type 2 diabetes mellitus.
- Continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus does not correspond to the ACT.

Table 2: Research questions of the benefit assessment of tirzepatide (multipage table)

Research question	Therapeutic indication[a]	ACT[b]
b. Presented is the respective ACT specified by the G-BA. c. For Research question 1, the options are the sulphonylureas of glibenclamide or glimepiride, which the G-BA rated as equivalent in the determination of the ACT. In the group of sulphonylureas, glipizide is pharmacologically and therapeutically comparable to glimepiride; in accordance with existing decisions concerning type 2 diabetes mellitus, it is therefore accepted as a comparator in studies. d. The indication for insulin therapy should be carefully verified. According to the guideline, insulin therapy is recommended if the individual treatment goal is not achieved despite intensification with other antidiabetic drugs, as well as in the case of metabolic derailments, administration of diabetogenic drugs (e.g. glucocorticoids), in the case of severely impaired renal function. Patients on insulin should be regularly examined to determine whether insulin therapy remains indicated or whether de-escalation of insulin therapy might be possible and indicated. According to the current generally recognized state of medical knowledge, insulin analogues are neither superior nor inferior to human insulin, but no long-term data are available showing any advantages of insulin analogues regarding hard outcomes. This benefit assessment also takes into account evidence from studies using insulin analogues, provided the results from studies with insulin analogues can be extrapolated to human insulin. The approval status of insulin analogues must be taken into account. If the studies were conducted with both human insulin and insulin analogues, study results should be analysed for possible effect modifications caused by the type of insulin used. Although the insulin analogue of insulin glargine was not explicitly listed as a component of the ACT, it was accepted as a suitable comparator in view of currently data situation. CT: conventional therapy; CHD: coronary heart disease; G-BA: Federal Joint Committee; GFR: glomerular filtration rate; ICT: intensified insulin therapy		

The company followed the G-BA's specification on the ACT for the respective research questions.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCT)s with a minimum duration of 24 weeks are used for the derivation of added benefit.

Research questions 1-4: insulin-naive adults with type 2 diabetes mellitus in whom diet and exercise and treatment with 1 or 2 blood glucose-lowering drugs do not provide adequate glycaemic control (without or with manifest cardiovascular disease)

Results on added benefit

No suitable data are available for the assessment of the added benefit of tirzepatide over the ACT in insulin-naive adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their previous drug therapy consisting of 1 or 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated. There is no hint of an added benefit of tirzepatide in comparison with the respective ACT; an added benefit is therefore not proven.

Research question 5: insulin-naive adults with type 2 diabetes mellitus in whom diet and exercise and treatment with at least 2 blood glucose-lowering drugs do not provide adequate glycaemic control and for whom insulin therapy is indicated (without manifest cardiovascular disease)

Results on added benefit

No suitable data are available for the assessment of the added benefit of tirzepatide in comparison with the ACT in insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated. There is no hint of an added benefit of tirzepatide in comparison with the ACT; an added benefit is therefore not proven.

Research question 6: insulin-naive adults with type 2 diabetes mellitus in whom diet and exercise and treatment with at least 2 blood glucose-lowering drugs do not provide adequate glycaemic control and for whom insulin therapy is indicated (with manifest cardiovascular disease)

Results

No relevant study was identified from the check of the completeness of the study pool. Deviating from this, the company identified the SURPASS-4 study and included it in its assessment. However, the study was unsuitable for the assessment of the added benefit of tirzepatide in insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved sufficient glycaemic control with their ongoing drug treatment consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated. The reasons are explained below.

SURPASS-4 study

The SURPASS-4 study is an open-label, randomized, active-controlled, 4-arm study with a treatment duration of 52 weeks and a variable treatment phase from Week 52 to Week 104. The study included adults with type 2 diabetes mellitus and glycated haemoglobin levels (HbA1c levels) between ≥ 7.5% and ≤ 10.5% at study inclusion despite at least 3 months of treatment with 1 to 3 oral antidiabetics in stable doses (metformin, sodium-glucose cotransporter 2 [SGLT2] inhibitors and/or sulfonylureas were permitted). The patients had to have an increased risk of cardiovascular events.

The SURPASS-4 study investigated the comparison of tirzepatide 5 mg, 10 mg, 15 mg with insulin glargine (U100), each in combination with the previously used oral antidiabetics (metformin, SGLT2 inhibitors, sulphonylureas). For the study, a total of 2002 patients were randomly assigned in a ratio of 1:1:1:3 to the 4 treatment arms tirzepatide 5 mg (N = 329), tirzepatide 10 mg (N = 330), tirzepatide 15 mg (N = 338) and insulin glargine (U100; N = 1005).

Randomization was stratified by country, baseline HbA1c value (≤ 8.5% or > 8.5%) and use of an SGLT2 inhibitor at baseline (yes or no). The company presented data from a subpopulation of the SURPASS-4 study: patients who were pretreated with a combination of metformin + empagliflozin or metformin + dapagliflozin (N = 229).

Primary outcome of the study was the change in HbA1c after 52 weeks compared with baseline. Secondary outcomes comprised outcomes from the categories of mortality, morbidity and side effects.

Treatment with the study medication

The starting dose of tirzepatide in the study was 2.5 mg once weekly over a period of 4 weeks. The starting dose was then increased by 2.5 mg every 4 weeks according to a dose escalation scheme until the patients had reached the maintenance dose allocated to them at randomization. This approach does not correspond to a needs-based increase or adjustment of the dose as specified in the Summary of Product Characteristics (SPC).

Patients in the comparator arm received insulin therapy consisting of insulin glargine (U100) and had to titrate their fasting blood glucose to a value of < 100 mg/dL. The insulin dose was adjusted once a week according to a specified titration scheme and was based on the median value of the last 3 self-measured fasting blood glucose values. This strict titration to a target value of < 100 mg/dL was only specified in the comparator arm.

The patients in the subpopulation of the SURPASS-4 study presented by the company also continued to receive their previous treatment with metformin + empagliflozin or metformin + dapagliflozin in the intervention and the comparator arm.

SURPASS-4 study unsuitable for the benefit assessment

No definition of individualized treatment goals

The German National Care Guideline on type 2 diabetes mellitus specifies an HbA1c target corridor between 6.5% and 8.5%, but individualized treatment goals for the HbA1c value should be agreed as part of the treatment of type 2 diabetes mellitus (recommendation grade A), as patients benefit from different target values. The individualized target ranges for HbA1c are influenced by various factors and must be agreed with the patient and adapted to their individual needs and everyday life. Furthermore, it is necessary to repeatedly review the therapy goals during the course of treatment.

In the SURPASS-4 study, however, no individualized HbA1c target values were agreed either at the start of the study or during its course. Instead, patients in the tirzepatide arms of the study were adjusted to a fixed dose (5 mg/10 mg/15 mg). Patients in the comparator arm had to titrate their fasting blood glucose values to a fixed target value of < 100 mg/dL by adjusting the insulin dose. This titration of insulin glargine to a fasting blood glucose value of < 100

mg/dL is neither found in the SPC for insulin glargine nor in the recommendations of the German National Care Guideline or in the practice recommendations of the German Diabetes Association cited by the company. In addition, strict titration of fasting blood glucose to a value of < 100 mg/dL was only specified in the comparator arm. Such different therapy goals between the treatment groups lead to an unfair and therefore uninterpretable comparison within the study, e.g. with regard to the frequency of hypoglycaemia occurring during the study. For these reasons, the SURPASS-4 study is not suitable for the benefit assessment.

Indication for insulin therapy questionable in the subpopulation presented

According to the ACT defined by the G-BA, insulin therapy must be indicated for patients in the present Research question 6. However, the indication for insulin therapy was not an explicit inclusion criterion of the SURPASS-4 study. It is unclear whether all drug measures other than insulin had already been exhausted for the patients included. Therefore, there is uncertainty as to whether the subpopulation presented by the company fulfils the criteria for Research question 6.

Results on added benefit

No suitable data are available for the assessment of the added benefit of tirzepatide over the ACT in insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated. There is no hint of an added benefit of tirzepatide in comparison with the ACT; an added benefit is therefore not proven.

Research questions 7 and 8: insulin-experienced adults with type 2 diabetes mellitus in whom diet and exercise and treatment with insulin do not provide adequate glycaemic control (without or with manifest cardiovascular disease)

Results

No relevant study was identified from the check of the completeness of the study pool. Deviating from this, the company identified the SURPASS-6 study and included it in its assessment. However, the study is not suitable for assessing the added benefit of tirzepatide in insulin-experienced adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their previous insulin regimen in addition to diet and exercise. The reasons are explained below.

SURPASS-6 study

The SURPASS-6 study is an open-label, randomized active-controlled 4-arm study with a treatment duration of 52 weeks. The study included adults with type 2 diabetes mellitus in whom the HbA1c value at study inclusion was between ≥ 7.5% and ≤ 11% despite at least 90

days of pre-treatment with a basal insulin and up to 2 oral antidiabetics (≥ 1500 mg/day metformin, sulphonylureas, dipeptidyl peptidase-4 [DPP-4] inhibitor).

The SURPASS-6 study compared tirzepatide 5 mg, 10 mg, 15 mg with insulin lispro (U100), in each case in combination with insulin glargine (U100) and possibly metformin (hereinafter referred to as tirzepatide + insulin glargine ± metformin or insulin lispro + insulin glargine ± metformin). For the study, a total of 1428 patients were randomly assigned in a ratio of 1:1:1:3 to the 4 treatment arms tirzepatide 5 mg + insulin glargine ± metformin (N = 243), tirzepatide 10 mg + insulin glargine ± metformin (N = 238), tirzepatide 15 mg + insulin glargine ± metformin (N = 236) or insulin lispro + insulin glargine ± metformin (N = 711). Randomization was stratified by country, baseline HbA1c value (≤ 8.5% or > 8.5%) and use of metformin at baseline (yes or no). In the dossier, the company presented 2 subpopulations of the SURPASS-6 study in accordance with the subdivision of the therapeutic indication by the G-BA: patients without manifest cardiovascular disease (N = 1171) and patients with manifest cardiovascular disease (N = 257).

Primary outcome of the study was the change in HbA1c after 52 weeks compared with baseline. Secondary outcomes comprised outcomes from the categories of mortality, morbidity, health-related quality of life and side effects.

Treatment with the study medication

Before randomization and the start of study treatment, patients had to optimize their insulin glargine therapy. The target range for fasting blood glucose was 100 to 125 mg/dL. Patients who were being treated with an insulin regimen other than insulin glargine (U100) or with sulphonylureas or DPP-4 inhibitors before entering the study had to switch their therapy to insulin glargine (U100).

The starting dose of tirzepatide in the study was 2.5 mg once weekly over a period of 4 weeks. The starting dose was then increased by 2.5 mg every 4 weeks according to a dose escalation scheme until the patients had reached the maintenance dose allocated to them at randomization. This approach does not correspond to a needs-based increase or adjustment of the dose as specified in the SPC.

Administration of insulin glargine (U100) and insulin lispro (U100) complies with the specifications of the respective SPC. A target range for fasting blood glucose of 100 to 125 mg/dl was specified in all treatment arms. The patients had to adjust their insulin dose according to a specified titration scheme. The basis for all dose adjustments was the median of the last 3 self-measured fasting blood glucose values.

For patients in the SURPASS-6 study, the continuation of their respective metformin therapy at a dose of ≥ 1500 mg/day up to the maximum dose according to country-specific approval was additionally planned in all study arms.

The use of GLP-1 receptor agonists, DPP-4 inhibitors and pramlintide was generally prohibited in the SURPASS-6 study. SGLT2 inhibitors were not permitted, neither as pre-treatment up to 90 days before screening nor as concomitant treatment during the study, except as rescue therapy for severe persistent hyperglycaemia, during safety follow-up or in the event of permanent discontinuation of study medication.

SURPASS-6 study unsuitable for the benefit assessment

No definition of individualized treatment goals

The German National Care Guideline on type 2 diabetes mellitus specifies an HbA1c target corridor between 6.5% and 8.5%, but individualized treatment goals for the HbA1c value should be agreed as part of the treatment of type 2 diabetes mellitus (recommendation grade A), as patients benefit from different target values. Here, the individualized target ranges for HbA1c are influenced by various factors and must be agreed with the patient and adapted to their individual needs and everyday life. Furthermore, it is necessary to repeatedly review the therapy goals during the course of treatment.

In the SURPASS-6 study, however, no individualized HbA1c target values were agreed either at the start of the study or during its course. Rather, patients had to titrate their fasting blood glucose values to a fixed target range between 100 to 125 mg/dL by adjusting the insulin dose. The SURPASS-6 study is therefore unsuitable for the benefit assessment.

Inappropriate diabetes therapy for patients with manifest cardiovascular disease (Research question 8)

According to the current German National Care Guideline on type 2 diabetes mellitus, insulin-naive patients with type 2 diabetes mellitus and concomitant clinically relevant cardiovascular disease or high cardiovascular risk should be offered treatment with SGLT2 inhibitors (e.g. empagliflozin) or GLP-1 receptor agonists (e.g. liraglutide) in addition to metformin. If insulin therapy is indicated, the addition of basal insulin is also planned for this patient group. In addition, the guideline recommends continuing an existing therapy with metformin + SGLT2 inhibitor/GLP-1 receptor agonist as part of the escalation of insulin therapy by adding a short-acting insulin, as long as this is well tolerated.

In the SURPASS-6 study, however, the use of GLP-1 receptor agonists was generally not permitted and SGLT2 inhibitors were only allowed to be used as rescue therapy for severe persistent hyperglycaemia, during the safety follow-up or in the event of permanent discontinuation of the study medication. Prior therapy with SGLT2 inhibitors or GLP-1 receptor

agonists within 90 days prior to study inclusion was also permitted according to the inclusion criteria. Based on the available information, it must therefore be assumed that the prior therapy of the patients with type 2 diabetes mellitus and cardiovascular disease included in SURPASS-6 did not comply with the recommendations of the current German National Care Guideline for type 2 diabetes mellitus.

Results on added benefit

No suitable data are available for the assessment of the added benefit of tirzepatide compared with the ACT in insulin-experienced adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their previous insulin regimen in addition to diet and exercise. There is no hint of an added benefit of tirzepatide in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of tirzepatide.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Tirzepatide – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	Individualized therapy taking into account the treatment goal determined for the individual patient based on comorbidities, time since diabetes diagnosis, and potential risk factors for hypoglycaemia, selecting from: ▪ metformin + sulphonylurea (glibenclamide or glimepiride)[c] ▪ metformin + sitagliptin, ▪ metformin + empagliflozin, ▪ metformin + liraglutide	Added benefit not proven
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	▪ Metformin + empagliflozin or ▪ metformin + liraglutide or ▪ metformin + dapagliflozin	Added benefit not proven
3	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + sitagliptin or ▪ metformin + empagliflozin + liraglutide	Added benefit not proven
4	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug treatment consisting of 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + liraglutide or ▪ metformin + dapagliflozin + liraglutide	Added benefit not proven

Table 3: Tirzepatide – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**[a]	**ACT**[b]	**Probability and extent of added benefit**
5	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin[d] + metformin	Added benefit not proven
6	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin[d] + metformin + empagliflozin or ▪ human insulin[d] + metformin + dapagliflozin or ▪ human insulin[d] + metformin + liraglutide	Added benefit not proven
7	Insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (conventional therapy [CT], possibly + metformin or dulaglutide or intensified insulin therapy [ICT])d	Added benefit not proven
8	Insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved sufficient glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (CT, possibly + metformin or empagliflozin or liraglutide or dapagliflozin or ICT)d	Added benefit not proven

Table 3: Tirzepatide – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
a. Subdivision of the therapeutic indication according to the G-BA. ▫ It is assumed that pharmacotherapy is initiated only after failure of basic treatment alone (non-drug measures such as diet, exercise, etc.) and is always carried out in combination with said treatment. ▫ All guidelines relevant in the therapeutic indication cite drug therapy with metformin as the standard of care for patients with type 2 diabetes mellitus. ▫ Initial diabetes treatment is assumed to be metformin monotherapy. ▫ In case of inadequate glycaemic control under metformin monotherapy, guidelines recommend continuing metformin administration and intensifying treatment by adding another drug. Treatment regimens without metformin therefore require an explanation as to why metformin was contraindicated for the patient. ▫ As per the current metformin dosing recommendations, metformin is an option for an expanded patient population, including patients with moderate renal impairment (GFR ≥ 30 mL/min). Because compared to the total population, only a small percentage of patients with type 2 diabetes mellitus are contraindicated for metformin, patients with metformin contraindication were not designated as a separate group. ▫ Based on the results of cardiovascular outcome studies and the recommendations of the guideline, which show that the most robust data were shown in diabetic patients with existing cardiovascular disease, a distinction is made between patients with and without manifest cardiovascular disease when determining the ACT. The operationalization of the definition of patients with manifest cardiovascular disease should be based on criteria that are generally accepted and established in medical science. ▫ For the treatment of comorbidities in patients with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, coronary artery disease, etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be administered, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular disease characteristics of type 2 diabetes mellitus. ▫ Continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus does not correspond to the ACT. b. Presented is the respective ACT specified by the G-BA. c. For Research question 1, the options are the sulphonylureas of glibenclamide or glimepiride, which the G-BA rated as equivalent in the determination of the ACT. In the group of sulphonylureas, glipizide is pharmacologically and therapeutically comparable to glimepiride; in accordance with existing decisions concerning type 2 diabetes mellitus, it is therefore accepted as a comparator in studies. d. The indication for insulin therapy should be carefully considered. According to the guideline, insulin therapy is recommended if the individual treatment goal is not achieved despite intensification with other antidiabetic drugs, as well as in the case of metabolic derailments, administration of diabetogenic drugs (e.g. glucocorticoids), in the case of severely impaired renal function. Patients on insulin should be regularly examined to determine whether insulin therapy remains indicated or whether de-escalation of insulin therapy might be possible and indicated. According to current medical knowledge, insulin analogues are neither superior nor inferior to human insulin, but no long-term data are available showing any advantages of insulin analogues regarding hard outcomes. This benefit assessment also takes into account evidence from studies using insulin analogues, provided the results from studies with insulin analogues can be extrapolated to human insulin. The approval status of insulin analogues must be taken into account. If the studies were conducted with both human insulin and insulin analogues, study results should be analysed for possible effect modifications caused by the type of insulin used. Although the insulin analogue of insulin glargine was not explicitly listed as a component of the ACT, it was accepted as a suitable comparator in view of currently available data.			

Table 3: Tirzepatide – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
CT: conventional therapy; CHD: coronary heart disease; G-BA: Federal Joint Committee; GFR: glomerular filtration rate; ICT: intensified insulin therapy			

The G-BA decides on the added benefit.

I 1.1 Research question

The aim of this report is to assess the added benefit of tirzepatide as an adjunct to diet and exercise in adult patients with inadequately controlled type 2 diabetes mellitus in comparison with the ACT

- as monotherapy if the use of metformin is not indicated due to intolerances or contraindications
- as add-on therapy to other diabetes mellitus drugs.

The research questions shown in Table 4 result from the ACT specified by the G-BA. The G-BA created no separate research question for tirzepatide as monotherapy based on the assumption that, compared to the total population, only a small percentage of patients with type 2 diabetes mellitus are contraindicated for metformin.

Table 4: Research questions of the benefit assessment of tirzepatide (multipage table)

Research question	**Therapeutic indication**[a]	**ACT**[b]
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	Individualized therapy taking into account the treatment goal determined for the individual patient based on comorbidities, time since diabetes diagnosis and potential risk factors for hypoglycaemia, selecting from: ▪ metformin + sulphonylurea (glibenclamide or glimepiride)[c], ▪ metformin + sitagliptin, ▪ metformin + empagliflozin, ▪ metformin + liraglutide
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	▪ Metformin + empagliflozin or ▪ metformin + liraglutide or ▪ metformin + dapagliflozin
3	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + sitagliptin or ▪ metformin + empagliflozin + liraglutide
4	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved sufficient glycaemic control with their ongoing drug treatment consisting of 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is not indicated	▪ metformin + empagliflozin + liraglutide or ▪ metformin + dapagliflozin + liraglutide
5	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin[d] + metformin

Table 4: Research questions of the benefit assessment of tirzepatide (multipage table)

Research question	**Therapeutic indication[a]**	**ACT[b]**
6	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin[d] + metformin + empagliflozin or ▪ human insulind + metformin + dapagliflozin or ▪ human insulind + metformin + liraglutide
7	Insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (CT, possibly + metformin or dulaglutide or ICT)[d]
8	Insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved sufficient glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (CT, possibly + metformin or empagliflozin or liraglutide or dapagliflozin or ICT)[d]

Table 4: Research questions of the benefit assessment of tirzepatide (multipage table)

Research question	Therapeutic indication[a]	ACT[b]

a. Subdivision of the therapeutic indication according to the G-BA.

- It is assumed that pharmacotherapy is initiated only after failure of basic treatment alone (non-drug measures such as diet, exercise, etc.) and is always carried out in combination with said treatment.
- All guidelines relevant in the therapeutic indication cite drug therapy with metformin as the standard of care for patients with type 2 diabetes mellitus.
- Initial diabetes treatment is assumed to be metformin monotherapy.
- In case of inadequate glycaemic control under metformin monotherapy, guidelines recommend continuing metformin administration and intensifying treatment by adding another drug. Treatment regimens without metformin therefore require an explanation as to why metformin was contraindicated for the patient.
- As per the current metformin dosing recommendation [3], metformin is an option for a broader patient population, including patients with moderate renal impairment (GFR ≥ 30 mL/min). Because compared to the total population, only a small percentage of patients with type 2 diabetes mellitus are contraindicated for metformin, patients with metformin contraindication were not designated as a separate group.
- Based on the results of cardiovascular outcome studies and the recommendations of the guideline [4], which show that the most robust data were shown in diabetic patients with existing cardiovascular disease, a distinction is made between patients with and without manifest cardiovascular disease when determining the ACT. The operationalization of the definition of patients with manifest cardiovascular disease should be based on criteria that are generally accepted and established in medical science.
- For the treatment of comorbidities in patients with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, CHD, etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be administered, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular disease characteristics of type 2 diabetes mellitus.
- Continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus does not correspond to the ACT.

b. Presented is the respective ACT specified by the G-BA.

c. For Research question 1, the options are the sulphonylureas of glibenclamide or glimepiride, which the G-BA rated as equivalent in the determination of the ACT. In the group of sulphonylureas, glipizide is pharmacologically and therapeutically comparable to glimepiride; in accordance with existing decisions concerning type 2 diabetes mellitus, it is therefore accepted as a comparator in studies.

d. The indication for insulin therapy should be carefully verified. According to the guideline [4], insulin therapy is recommended if the individual treatment goal is not achieved despite intensification with other antidiabetic drugs, as well as in the case of metabolic derailments, administration of diabetogenic drugs (e.g. glucocorticoids), in the case of severely impaired renal function.
Patients on insulin should be regularly examined to determine whether insulin therapy remains indicated or whether de-escalation of insulin therapy might be possible and indicated.
According to current medical knowledge, insulin analogues are neither superior nor inferior to human insulin, but no long-term data are available showing any advantages of insulin analogues regarding hard outcomes. This benefit assessment also takes into account evidence from studies using insulin analogues, provided the results from studies with insulin analogues can be extrapolated to human insulin. The approval status of insulin analogues must be taken into account. If the studies were conducted with both human insulin and insulin analogues, study results should be analysed for possible effect modifications caused by the type of insulin used.
Although the insulin analogue of insulin glargine was not explicitly listed as a component of the ACT, it was accepted as a suitable comparator in view of currently available data.

Table 4: Research questions of the benefit assessment of tirzepatide (multipage table)

Research question	Therapeutic indication[a]	ACT[b]
CT: conventional therapy; CHD: coronary heart disease; G-BA: Federal Joint Committee; GFR: glomerular filtration rate; ICT: intensified insulin therapy		

The company followed the G-BA's specification on the ACT for the respective research questions.

In this benefit assessment, the subpopulations a1, a2, b1, b2, c1, c2, d1 and d2 named by the G-BA and the company, are referred to as Research questions 1 to 8 in accordance with the research questions in Table 4.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company’s inclusion criteria.

In the following, Research questions 1 to 5 are addressed first, for which the company presented no data; Research questions 1 to 4 are addressed together. This is followed by Research question 6 and Research questions 7 and 8, which are addressed together.

I 1.2 Research questions 1-4: insulin-naive adults with type 2 diabetes mellitus in whom diet and exercise and treatment with 1 or 2 blood glucose-lowering drugs do not provide adequate glycaemic control (without or with manifest cardiovascular disease)

I 1.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on tirzepatide (status: 05 September 2023)
- bibliographical literature search on tirzepatide (last search on 05 September 2023)
- search in trial registries/trial results databases for studies on tirzepatide (last search on 05 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on tirzepatide (last search on 30 November 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no RCT for the direct comparison of tirzepatide with the ACT for Research questions 1 to 4 (insulin-naive adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their previous drug therapy consisting of 1 [Research questions 1 and 2] or 2 [Research questions 3 and 4] blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated).

I 1.4 Results on added benefit

No suitable data are available for the assessment of the added benefit of tirzepatide over the ACT in insulin-naive adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their previous drug therapy consisting of 1 or 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated. There is no hint of an added benefit of tirzepatide in comparison with the respective ACT; an added benefit is therefore not proven.

I 1.5 Probability and extent of added benefit

As the company presented no suitable data for the assessment of the added benefit of tirzepatide in comparison with the ACT in insulin-naive adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their previous drug therapy consisting of 1 or 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated, an added benefit is not proven for these patients.

The assessment described above concurs with that of the company.

I 1.6 Research question 5: insulin-naive adults with type 2 diabetes mellitus in whom diet and exercise and treatment with at least 2 blood glucose-lowering drugs do not provide adequate glycaemic control and for whom insulin therapy is indicated (without manifest cardiovascular disease)

I 1.7 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on tirzepatide (status: 05 September 2023)
- bibliographical literature search on tirzepatide (last search on 05 September 2023)
- search in trial registries/trial results databases for studies on tirzepatide (last search on 27 September 2023)
- search on the G-BA website for tirzepatide (last search on 27 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on tirzepatide (last search on 30 November 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check for completeness of the study pool identified no RCT on the direct comparison of tirzepatide with the ACT for Research question 5 (insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated).

I 1.8 Results on added benefit

No suitable data are available for the assessment of the added benefit of tirzepatide in comparison with the ACT in insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated. There is no hint of an added benefit of tirzepatide in comparison with the ACT; an added benefit is therefore not proven.

I 1.9 Probability and extent of added benefit

As the company presented no suitable data for the assessment of the added benefit of tirzepatide in comparison with the ACT in insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated, an added benefit is not proven for these patients.

The assessment described above concurs with that of the company.

I 1.10 Research question 6: Insulin-naive adults with type 2 diabetes mellitus in whom diet and exercise and treatment with at least 2 blood glucose-lowering drugs do not provide adequate glycaemic control and for whom insulin therapy is indicated (with manifest cardiovascular disease)

I 1.11 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on tirzepatide (status: 05 September 2023)

- bibliographical literature search on tirzepatide (last search on 05 September 2023)
- search in trial registries/trial results databases for studies on tirzepatide (last search on 27 September 2023)
- search on the G-BA website for tirzepatide (last search on 27 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on tirzepatide (last search on 30 November 2023); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check of the study pool.

The company includes the study I8F-MC-GPGM (hereinafter referred to as SURPASS-4) [5-8] for Research question 6 (referred to by the company as Research question c2 in the dossier). However, the SURPASS-4 study is not suitable for assessing the added benefit of tirzepatide in insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated, mainly because no patient-specific target values for the glycated haemoglobin level (HbA1c value) had been agreed. This is explained below. For this purpose, the SURPASS-4 study is described first.

SURPASS-4 study

The SURPASS-4 study is an open-label, randomized active-controlled 4-arm study with a treatment duration of 52 weeks and a variable treatment phase from Week 52 to Week 104 (see also I Appendix B). The study included adults with type 2 diabetes mellitus in whom the HbA1c value at study inclusion was between ≥ 7.5% and ≤ 10.5% despite at least 3 months of treatment with 1 to 3 oral antidiabetics at a stable dose (metformin, SGLT2 inhibitors and/or sulphonylureas were permitted). The patients had to have an increased risk of cardiovascular events. In the SURPASS-4 study, this was operationalized as follows: coronary heart disease; peripheral arterial occlusive disease or cerebrovascular disease, each with atherosclerotic genesis; chronic kidney disease or heart failure (New York Heart Association [NYHA] classes II to III) in conjunction with an age ≥ 50 years. Patients who had experienced a myocardial infarction, stroke or hospitalization due to heart failure within 2 months prior to study inclusion or who had NYHA class IV heart failure were excluded from the study. Furthermore, patients had to have a body mass index (BMI) of ≥ 25 kg/m^2 and agree not to start a diet or exercise programme with the aim of losing weight during the study, with the exception of lifestyle changes and dietary habits for diabetes treatment.

The SURPASS-4 study investigated the comparison of tirzepatide 5 mg, 10 mg, 15 mg with insulin glargine (U100), each in combination with the previously used oral antidiabetics

(metformin, SGLT2 inhibitors, sulphonylureas). For the study, a total of 2002 patients were randomly assigned in a ratio of 1:1:1:3 to the 4 treatment arms tirzepatide 5 mg (N = 329), tirzepatide 10 mg (N = 330), tirzepatide 15 mg (N = 338) and insulin glargine (U100; N = 1005). Randomization was stratified by country, baseline HbA1c value (≤ 8.5% or > 8.5%) and use of an SGLT2 inhibitor at baseline (yes or no). The company presented data from a subpopulation of the SURPASS-4 study: patients who were pretreated with a combination of metformin + empagliflozin or metformin + dapagliflozin. This resulted in the following study arms: tirzepatide (5 mg, 10 mg, 15 mg) + metformin + empagliflozin or dapagliflozin (n = 107) vs. insulin glargine (U100) + metformin + empagliflozin or dapagliflozin (n = 122). According to the company, cardiovascular disease was present in approx. 88% vs. 90% of patients in the intervention or the comparator arm.

Primary outcome of the study was the change in HbA1c after 52 weeks compared with baseline. Secondary outcomes comprised outcomes from the categories of mortality, morbidity and side effects.

Treatment with the study medication

In the SURPASS-4 study, patients were randomly assigned to a tirzepatide dose of 5 mg, 10 mg or 15 mg. The starting dose of tirzepatide in the study was 2.5 mg once weekly over a period of 4 weeks. The starting dose was then increased by 2.5 mg every 4 weeks according to a dose escalation scheme until the patients had reached the maintenance dose allocated to them at randomization. If intolerable gastrointestinal symptoms occurred, the investigator could decide to reduce the tirzepatide dose once to the next lower maintenance dose (5 mg or 10 mg) during the dose escalation phase (weeks 0 to 24). The patients then received the lower tirzepatide dose for the remaining study duration. Further individualized dose adjustments of tirzepatide were not permitted. This approach does not correspond to a needs-based increase or adjustment of the dose as specified in the SPC [9].

Patients in the comparator arm received insulin therapy consisting of insulin glargine (U100) and had to titrate their fasting blood glucose to a value of < 100 mg/dL. The insulin dose was adjusted once a week according to a specified titration scheme and was based on the median value of the last 3 self-measured fasting blood glucose values. This strict titration to a target value of < 100 mg/dL was only specified in the comparator arm.

The patients in the subpopulation of the SURPASS-4 study presented by the company also continued to receive their previous treatment with metformin + empagliflozin or metformin + dapagliflozin in the intervention and the comparator arm. The use of GLP-1 receptor agonists, DPP-4 inhibitors and amylin analogues was generally prohibited. Other blood glucose-lowering drugs could be prescribed at the discretion of the investigator as part of a rescue therapy for severe persistent hyperglycaemia.

No definition of individualized treatment goals

The HbA1c value reflects the average blood glucose level of the last 8 to 12 weeks and is an important target value in the treatment of type 2 diabetes mellitus. For example, it can be used to assess the success of the therapy and help to discover whether an intensification of the therapy is indicated. The German National Care Guideline on type 2 diabetes mellitus [4] specifies an HbA1c target corridor between 6.5% and 8.5%, but individualized treatment targets for the HbA1c value should be agreed as part of the treatment of type 2 diabetes mellitus (recommendation grade A), as patients benefit from different target values. The individualized HbA1c target ranges are influenced by various factors, such as age, physical condition, comorbidities, time since diabetes diagnosis, treatment adherence, treatment level and risk of hypoglycaemia and other adverse events [4]. Treatment goals must therefore be agreed together with the patients and tailored to their individual needs and everyday life. Furthermore, it is necessary to repeatedly review the treatment goals during the course of treatment, as these can shift due to changes in the patient's life situation [4].

In the SURPASS-4 study, however, no individualized HbA1c target values were agreed either at the start of the study or during its course. This approach is not appropriate and does not comply with the previously described recommendations of the German National Care Guideline [4] for setting individualized HbA1c target values. Instead, patients in the tirzepatide arms of the study were adjusted to a fixed dose (5 mg/10 mg/15 mg). Patients in the comparator arm had to titrate their fasting blood glucose values to a fixed target value of < 100 mg/dL by adjusting the insulin dose. This titration of insulin glargine to a fasting blood glucose value of < 100 mg/dL is neither found in the SPC for insulin glargine [10] nor in the recommendations of the German National Care Guideline [4] or in the practice recommendations of the German Diabetes Association cited by the company [11]. In the latter, higher fasting blood glucose values of between 100 and 125 mg/dL are given as reference values within the framework of individually agreed treatment goals. The company itself notes in Module 4 C of its dossier on the titration algorithm that the target values in the SURPASS-4 study are somewhat lower than those in the practice recommendations of the German Diabetes Association. In addition, strict titration of fasting blood glucose to a value of < 100 mg/dL was only specified in the comparator arm. Such different therapy goals between the treatment groups lead to an unfair and therefore uninterpretable comparison within the study, e.g. with regard to the frequency of hypoglycaemia occurring during the study. For these reasons, the SURPASS-4 study is not suitable for the benefit assessment.

Indication for insulin therapy questionable in the subpopulation presented

According to the subdivision of the therapeutic indication by the ACT defined by the G-BA, insulin therapy must be indicated for patients in the present Research question 6. However, the indication for insulin therapy was not an explicit inclusion criterion of the SURPASS-4 study. According to the German National Care Guideline [4], insulin therapy is only

recommended if the individual therapy goal is not achieved despite exhausting non-drug measures and drug therapy (combination of oral antidiabetics ± subcutaneous GLP-1 receptor agonists). The subpopulation presented by the company had received pretreatment consisting of 2 oral antidiabetics each, metformin + empagliflozin or metformin + dapagliflozin, before inclusion in the study and before intensification of therapy with tirzepatide or insulin glargine. It is unclear whether all drug measures other than insulin had already been exhausted for these patients. If necessary, a triple combination of metformin + SGLT2 inhibitor (empagliflozin or dapagliflozin) + GLP-1 receptor agonist (e.g. liraglutide) is indicated as an intensification of therapy before the start of insulin administration. Information on prior therapies for the entire study population (N = 2002) shows that < 2% of patients had received liraglutide prior to study inclusion. The subpopulation presented by the company would thus rather correspond to Research question 4 (patients with manifest cardiovascular disease who do not yet have an indication for insulin therapy and have received 2 blood glucose-lowering drugs in the previous therapy), for whom the G-BA envisages treatment with a triple combination of metformin + SGLT2 inhibitor (empagliflozin or dapagliflozin) + liraglutide as ACT. Therefore, there is uncertainty as to whether the subpopulation presented by the company meets the criteria for Research question 6.

The SURPASS-4 study was conducted as a multi-centre study in Australia, North America, South America, Europe and Asia, and in different countries within each continent. It can therefore be assumed that health care standards are very heterogeneous and deviate from the German health care context.

Overall, the SURPASS-4 study is unsuitable for the benefit assessment of tirzepatide in addition to other drugs in insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their ongoing drug treatment consisting of at least 2 blood-glucose lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated.

I 1.12 Results on added benefit

No suitable data are available for the assessment of the added benefit of tirzepatide over the ACT in insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated. There is no hint of an added benefit of tirzepatide in comparison with the ACT; an added benefit is therefore not proven.

I 1.13 Probability and extent of added benefit

As the company presented no suitable data for the assessment of the added benefit of tirzepatide in comparison with the ACT in insulin-naive adults with type 2 diabetes mellitus

with manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated, an added benefit is not proven for these patients.

The assessment described above deviates from that of the company, which, on the basis of the SURPASS-4 study, derived an indication of considerable added benefit for insulin-naive adults with manifest cardiovascular disease who have not achieved sufficient blood glucose control with their previous drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated.

I 2 Research questions 7 and 8: insulin-experienced adults with type 2 diabetes mellitus in whom diet and exercise and treatment with insulin do not provide adequate glycaemic control (without or with manifest cardiovascular disease)

I 2.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on tirzepatide (status: 05 September 2023)
- bibliographical literature search on tirzepatide (last search on 05 September 2023)
- search in trial registries/trial results databases for studies on tirzepatide (last search on 27 September 2023)
- search on the G-BA website for tirzepatide (last search on 27 September 2023)
- To check the completeness of the study pool:
- search in trial registries for studies on tirzepatide (last search on 30 November 2023); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check of the study pool.

The company includes the I8F-MC-GPHD study (hereinafter referred to as SURPASS-6) [12-15] for Research questions 7 and 8 (referred to by the company in the dossier as Research questions d1 and d2). However, the SURPASS-6 study is not suitable for assessing the added benefit of tirzepatide in insulin-experienced adults with type 2 diabetes mellitus (without or with manifest cardiovascular disease) who have not achieved adequate glycaemic control with their previous insulin regimen in addition to diet and exercise, mainly because no patient-specific target values for the HbA1c value had been agreed. This is explained below. For this purpose, the SURPASS-6 study is described first.

SURPASS-6 study

The SURPASS-6 study is an open-label, randomized active-controlled 4-arm study with a treatment duration of 52 weeks (see also I Appendix C). The study included adults with type 2 diabetes mellitus in whom the HbA1c value at study inclusion was between ≥ 7.5% and ≤ 11% despite at least 90 days of prior treatment with a basal insulin and up to 2 oral antidiabetics (≥ 1500 mg/day metformin, sulphonylureas, DPP-4 inhibitor). Furthermore, patients had to have a BMI of ≥ 23 kg/m^2 to ≤ 45 kg/m^2 and agree not to start a diet or exercise programme with the aim of losing weight during the study, with the exception of lifestyle changes and dietary habits for diabetes treatment. Patients with cardiovascular disease or at high cardiovascular risk were not categorically excluded from the SURPASS-6 study. Patients who

had experienced a myocardial infarction, stroke or hospitalization due to heart failure within 2 months prior to study inclusion were explicitly excluded from the study. In addition, the presence of NYHA class III or IV heart failure was considered an exclusion criterion.

The SURPASS-6 study compared tirzepatide 5 mg, 10 mg, 15 mg with insulin lispro (U100), in each case in combination with insulin glargine (U100) and possibly metformin (hereinafter referred to as tirzepatide + insulin glargine ± metformin or insulin lispro + insulin glargine ± metformin). For the study, a total of 1428 patients were randomly assigned in a ratio of 1:1:1:3 to the 4 treatment arms tirzepatide 5 mg + insulin glargine ± metformin (N = 243), tirzepatide 10 mg + insulin glargine ± metformin (N = 238), tirzepatide 15 mg + insulin glargine ± metformin (N = 236) or insulin lispro + insulin glargine ± metformin (N = 711). Randomization was stratified by country, baseline HbA1c value (≤ 8.5% or > 8.5%) and use of metformin at baseline (yes or no). In the dossier, the company presented 2 subpopulations of the SURPASS-6 study in accordance with the subdivision of the therapeutic indication by the G-BA: patients without manifest cardiovascular disease (d1 according to the company; corresponds to Research question 7) and patients with manifest cardiovascular disease (d2 according to the company; corresponds to Research question 8). A large proportion of patients in the study had no manifest cardiovascular disease (82%). This subpopulation comprised 584 patients treated with tirzepatide (5 mg, 10 mg, 15 mg) + insulin glargine ± metformin and 587 patients treated with insulin lispro + insulin glargine ± metformin. The proportion of patients with manifest cardiovascular disease was 18% and comprised 133 patients in the intervention arm and 124 patients in the comparator arm.

Primary outcome of the study was the change in HbA1c after 52 weeks compared with baseline. Secondary outcomes comprised outcomes from the categories of mortality, morbidity, health-related quality of life and side effects.

Treatment with the study medication

Before randomization and the start of study treatment, patients had to optimize their insulin glargine therapy. The target range for fasting blood glucose was 100 to 125 mg/dL. Patients who were being treated with an insulin regimen other than insulin glargine (U100) or with sulphonylureas or DPP-4 inhibitors before entering the study had to switch their therapy to insulin glargine (U100). At the start of the study treatment, the insulin glargine-dose was temporarily reduced by 30% in both arms to avoid the risk of hypoglycaemia. Insulin glargine (U100) was then titrated according to a predetermined titration scheme.

In the SURPASS-6 study, patients were randomly assigned to a tirzepatide dose of 5 mg, 10 mg or 15 mg. The starting dose of tirzepatide in the study was 2.5 mg once weekly over a period of 4 weeks. The starting dose was then increased by 2.5 mg every 4 weeks according to a dose escalation scheme until the patients had reached the maintenance dose allocated to them at

randomization. Individualized dose adjustments of tirzepatide were not permitted. This approach does not correspond to a needs-based increase or adjustment of the dose as specified in the SPC [9].

Administration of insulin glargine (U100) and insulin lispro (U100) complied with the specifications of the respective SPC [10,16]. A target range for fasting blood glucose of 100 to 125 mg/dL was specified in all treatment arms. The patients had to adjust their insulin dose according to a specified titration scheme. The dose of insulin glargine (U100) was adjusted once a week. In the comparator arm, the dose of insulin lispro (U100) was adjusted twice a week up to Week 24, after which the adjustment could be reduced to once a week at the investigator's discretion. The basis for all dose adjustments was the median of the last 3 self-measured fasting blood glucose values.

For patients in the SURPASS-6 study, the continuation of their respective metformin therapy at a dose of ≥ 1500 mg/day up to the maximum dose according to country-specific approval was additionally planned in all study arms. In Germany, the maximum recommended daily dose is 3000 mg [17]. Module 4 D of the dossier provides no information on the metformin dosage received by the patients.

The use of GLP-1 receptor agonists, DPP-4 inhibitors and pramlintide was generally not permitted in the SURPASS-6 study. Basal insulins other than insulin glargine (U100) and prandial insulins other than insulin lispro (U100) were only allowed to be used for short periods (≤ 14 days) and only under certain clinical circumstances, e.g. hospitalization, elective surgery or hyperosmolar conditions. SGLT2 inhibitors were not permitted, neither as pre-treatment up to 90 days before screening nor as concomitant treatment during the study, except as rescue therapy for severe persistent hyperglycaemia, during safety follow-up or in the event of permanent discontinuation of study medication.

No definition of individualized treatment goals

The HbA1c value reflects the average blood glucose level of the last 8 to 12 weeks and is an important target value in the treatment of type 2 diabetes mellitus. For example, it can be used to assess the success of the therapy and help to discover whether an intensification of the therapy is indicated. The German National Care Guideline for type 2 diabetes mellitus [4] specifies an HbA1c target corridor between 6.5% and 8.5%, but individualized treatment targets for the HbA1c value should be agreed as part of the treatment of type 2 diabetes mellitus (recommendation grade A), as patients benefit from different target values. The individualized HbA1c target ranges are influenced by various factors, such as age, physical condition, comorbidities, time since diabetes diagnosis, treatment adherence, treatment level and risk of hypoglycaemia and other adverse effects [4]. Treatment goals must therefore be agreed together with the patients and tailored to their individual needs and everyday life.

Furthermore, it is necessary to repeatedly review the treatment goals during the course of treatment, as these can shift due to changes in the patient's life situation [4].

In the SURPASS-6 study, however, no individualized HbA1c target values were agreed either at the start of the study or during its course. This approach is not appropriate and does not comply with the previously described recommendations of the German National Care Guideline [4] for setting individualized HbA1c target values. Rather, patients had to titrate their fasting blood glucose values to a fixed target range between 100 to 125 mg/dL by adjusting the insulin dose. The SURPASS-6 study is therefore unsuitable for the benefit assessment.

Inappropriate diabetes therapy for patients with manifest cardiovascular disease (Research question 8)

According to the current German National Care Guideline for type 2 diabetes mellitus [4], insulin-naive patients with type 2 diabetes mellitus and concomitant clinically relevant cardiovascular disease or at high cardiovascular risk should be offered treatment with SGLT2 inhibitors (e.g. empagliflozin) or GLP-1 receptor agonists (e.g. liraglutide) in addition to metformin. If insulin therapy is indicated, the addition of basal insulin is also planned for this patient group. In addition, the guideline recommends continuing an existing therapy with metformin + SGLT2 inhibitor/GLP-1 receptor agonist as part of the escalation of insulin therapy by adding a short-acting insulin, as long as this is well tolerated.

In the SURPASS-6 study, however, the use of GLP-1 receptor agonists was generally not permitted and SGLT2 inhibitors were only allowed to be used as rescue therapy for severe persistent hyperglycaemia, during the safety follow-up or in the event of permanent discontinuation of the study medication. Only 1 patient with type 2 diabetes mellitus and manifest cardiovascular disease in the comparator arm received treatment with an SGLT2 inhibitor (empagliflozin) as rescue therapy. Foregoing the use of SGLT2 inhibitors or GLP-1 receptor agonists in the treatment of patients with type 2 diabetes mellitus and concomitant cardiovascular disease, as was done in the SURPASS-6 study, is inappropriate according to the current German National Care Guideline for type 2 diabetes mellitus [4]. Prior therapy with SGLT2 inhibitors or GLP-1 receptor agonists within 90 days prior to study inclusion was also permitted according to the inclusion criteria. According to the information provided in the study report [14], only a small proportion of 5.6% of the total study population (patients with and without manifest cardiovascular disease) in the intervention arm (tirzepatide 5 mg, 10 mg, 15 mg) vs. 4.2% in the comparator arm had ever received treatment with a GLP-1 receptor agonist prior to study inclusion; corresponding data for the treatment with an SGLT2 inhibitor are lacking. Based on the available information, it must therefore be assumed that the prior therapy of the patients with type 2 diabetes mellitus and cardiovascular disease included in SURPASS-6 did not comply with the recommendations of the current German National Care

Guideline for type 2 diabetes mellitus [4]. The SURPASS-6 study was conducted as a multi-centre study in North America, South America, Europe and Asia and in different countries within each continent. It can therefore be assumed that health care standards are very heterogeneous and deviate from the German health care context.

Overall, the SURPASS-6 study is unsuitable for the benefit assessment of tirzepatide in addition to other drugs in insulin-experienced adults with type 2 diabetes mellitus (without and with manifest cardiovascular disease) who have not achieved adequate glycaemic control with their ongoing insulin regimen in addition to diet and exercise.

I 2.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of tirzepatide compared with the ACT in insulin-experienced adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their previous insulin regimen in addition to diet and exercise. There is no hint of an added benefit of tirzepatide in comparison with the ACT; an added benefit is therefore not proven.

I 2.3 Probability and extent of added benefit

An added benefit for these patients is not proven as the company did not present suitable data for the assessment of the added benefit of tirzepatide compared with the ACT in insulin-experienced adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their previous insulin regimen in addition to diet and exercise.

The assessment described above deviates from that of the company, which, on the basis of the SURPASS-6 study, derived an indication of considerable added benefit for insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease (Research question 7) or with manifest cardiovascular disease (Research question 8), who have not achieved adequate glycaemic control with their previous insulin regimen in addition to diet and exercise.

I 3 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of tirzepatide in comparison with the ACT is summarized in Table 5.

Table 5: Tirzepatide – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication[a]**	**ACT[b]**	**Probability and extent of added benefit**
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	Individualized therapy taking into account the treatment goal determined for the individual patient based on comorbidities, time since diabetes diagnosis and potential risk factors for hypoglycaemia, selecting from: ▪ metformin + sulphonylurea (glibenclamide or glimepiride)[c], ▪ metformin + sitagliptin, ▪ metformin + empagliflozin, ▪ metformin + liraglutide	Added benefit not proven
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 1 blood glucose-lowering drug in addition to diet and exercise	▪ Metformin + empagliflozin or ▪ metformin + liraglutide or ▪ metformin + dapagliflozin	Added benefit not proven
3	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + sitagliptin or ▪ metformin + empagliflozin + liraglutide	Added benefit not proven
4	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug treatment consisting of 2 blood-glucose lowering drugs in addition to diet and exercise and for whom insulin therapy is not indicated	▪ Metformin + empagliflozin + liraglutide or ▪ metformin + dapagliflozin + liraglutide	Added benefit not proven

Table 5: Tirzepatide – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**[a]	**ACT**[b]	**Probability and extent of added benefit**
5	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin[d] + metformin	Added benefit not proven
6	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their current drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin[d] + metformin + empagliflozin or ▪ human insulin[d] + metformin + dapagliflozin or ▪ human insulin[d] + metformin + liraglutide	Added benefit not proven
7	Insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (CT, possibly + metformin or dulaglutide or ICT)[d]	Added benefit not proven
8	Insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved sufficient glycaemic control with their current insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (CT, possibly + metformin or empagliflozin or liraglutide or dapagliflozin or ICT)[d]	Added benefit not proven

Table 5: Tirzepatide – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit

a. Subdivision of the therapeutic indication according to the G-BA.

- It is assumed that pharmacotherapy is initiated only after failure of basic treatment alone (non-drug measures such as diet, exercise, etc.) and is always carried out in combination with said treatment.
- All guidelines relevant in the therapeutic indication cite drug therapy with metformin as the standard of care for patients with type 2 diabetes mellitus.
- Initial diabetes treatment is assumed to be metformin monotherapy.
- In case of inadequate glycaemic control under metformin monotherapy, guidelines recommend continuing metformin administration and intensifying treatment by adding another drug. Treatment regimens without metformin therefore require an explanation as to why metformin was contraindicated for the patient.
- As per the current metformin dosing recommendation [3], metformin is an option for a broader patient population, including patients with moderate renal impairment (GFR ≥ 30 mL/min). Because compared to the total population, only a small percentage of patients with type 2 diabetes mellitus are contraindicated for metformin, patients with metformin contraindication were not designated as a separate group.
- Based on the results of cardiovascular outcome studies and the recommendations of the guideline [4], which show that the most robust data were shown in diabetic patients with existing cardiovascular disease, a distinction is made between patients with and without manifest cardiovascular disease when determining the ACT. The operationalization of the definition of patients with manifest cardiovascular disease should be based on criteria that are generally accepted and established in medical science.
- For the treatment of comorbidities in patients with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, coronary artery disease, etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be administered, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular disease characteristics of type 2 diabetes mellitus.
- Continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus does not correspond to the ACT.

b. Presented is the respective ACT specified by the G-BA.

c. For Research question 1, the options are the sulphonylureas of glibenclamide or glimepiride, which the G-BA rated as equivalent in the determination of the ACT. In the group of sulphonylureas, glipizide is pharmacologically and therapeutically comparable to glimepiride; in accordance with existing decisions concerning type 2 diabetes mellitus, it is therefore accepted as a comparator in studies.

d. The indication for insulin therapy should be carefully considered. According to the guideline [4], insulin therapy is recommended if the individual treatment goal is not achieved despite intensification with other antidiabetic drugs, as well as in the case of metabolic derailments, administration of diabetogenic drugs (e.g. glucocorticoids), in the case of severely impaired renal function.
Patients on insulin should be regularly examined to determine whether insulin therapy remains indicated or whether de-escalation of insulin therapy might be possible and indicated.
According to the current generally recognized state of medical knowledge, insulin analogues are neither superior nor inferior to human insulin, but no long-term data are available showing any advantages of insulin analogues regarding hard outcomes. This benefit assessment also takes into account evidence from studies using insulin analogues, provided the results from studies with insulin analogues can be extrapolated to human insulin. The approval status of insulin analogues must be taken into account. If the studies were conducted with both human insulin and insulin analogues, study results should be analysed for possible effect modifications caused by the type of insulin used.
Although the insulin analogue of insulin glargine was not explicitly listed as a component of the ACT, it was accepted as a suitable comparator in view of currently available data.

Table 5: Tirzepatide – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**[a]	**ACT**[b]	**Probability and extent of added benefit**
CT: conventional therapy; CHD: coronary heart disease; G-BA: Federal Joint Committee; GFR: glomerular filtration rate; ICT: intensified insulin therapy			

The G-BA decides on the added benefit.

I 4 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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