Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an amendment of the Pharmaceuticals Directive (AM-RL): Appendix XII – Resolutions on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V Insulin degludec (Reassessment based on new scientific knowledge)

From 16. May 2019

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 was carried out based on evidence provided by the pharmaceutical manufacturer. This evidence, including all clinical trials that have been conducted or commissioned, must be submitted to the G-BA electronically at the latest when the medicinal product is placed on the market for the first time and when new indications for the medicinal product are authorised. In particular, it must contain the following information:

1st Approved therapeutic indications,

2nd Medicinal benefit,

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

4th Number of patients and patient groups experiencing a therapeutically significant additional benefit,

5th Costs of the treatment for the statutory health insurance,

6th Requirement for 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 and published on the Internet within three months of the relevant date for submission of evidence.

According to Section 35a paragraph 3 SGB V, the G-BA shall decide on the benefit assessment within three months of its publication. The resolution is to be published on the Internet and forms part of the Pharmaceuticals Directive.

2. Key points of the decision

The active ingredient insulin degludec as an active ingredient of the medicinal product Tresiba® was first placed on the (German) market on 1 May 2014. The G-BA prompted a new benefit assessment in accordance with 35a paragraph 1 in conjunction with Section 3 paragraph 1 no. 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) and Chapter 5, Section 13 Rules of Procedure [Verfahrensordnung (VerfO) for the active ingredient insulin degludec at the request of its members in the resolution of 15 February 2018. The renewed benefit assessment was prompted based on new scientific knowledge from the completed DEVOTE (NCT01959529) study. Tresiba® was not available on the German market in the meantime and was placed on the market again on 1 December 2018.

The relevant time in accordance with Chapter 5, Section 8, paragraph 1, number 6 of the Rules of Procedure of the G-BA (VerfO) is the time of placing the active ingredientInsulin degludec on the market again on 1. Dezember 2018. The pharmaceutical manufacturer submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1 number 6 VerfO. on 28. November 2018.

The G-BA has commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1. März 2019, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has taken its decision on the question whether an additional benefit of Insulin degludec compared to the appropriate comparator therapy can be determined based on the pharmaceutical manufacturer's dossier, the dossier assessment prepared by the IQWiG and the statements submitted for this purpose in the written and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the finding relevant for approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of Insulin degludec.

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

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

2.1.1 Approved therapeutic indication ofInsulin degludec (Tresiba®) in accordance with the product information

Treatment of diabetes mellitus in adults, young persons, and children aged 1 year and older.

NB: the new benefit assessment of insulin degludec relates exclusively to the therapeutic indication for the treatment of adults with type 2 diabetes mellitus

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

In the mono- or combination therapy

a) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

Appropriate comparator therapy

- Human insulin + metformin *or*
- Human insulin + empagliflozin[2] *or*
- Human insulin + liraglutide[2] *or*
- Human insulin if the particular combination partners in accordance with the product information are incompatible or contraindicated or not sufficiently effective because of an advanced type 2 diabetes mellitus

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

[1] General methods, Version 5.0 from 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

[2] Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-reducers (for the operationalisation, see study protocols: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–28. DOI 10.1056/NEJMoa1504720 or Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375: 311–322. DOI: 10.1056/NEJMoa1603827).

Appropriate comparator therapy

- The optimisation of the human insulin regimen (possibly + metformin *or* empagliflozin[2] *or* liraglutide[2])

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally accepted state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies exist and which has proven itself in practical application, except where required otherwise by guidelines pursuant to Section 92 paragraph 1 SGB V or the efficiency principle.

When determining the appropriate comparator therapy pursuant to Chapter 5, Section 6 paragraph 3 VerfO, the following criteria in particular must be taken into account:

1. If a drug application can be considered as a comparator therapy, the medicinal product in principle must have a marketing authorisation for the therapeutic indication.
2. If a non-drug treatment is deemed applicable as a comparator therapy, this must be covered by the SHI.
3. Drug applications or non-drug treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred as a comparator therapy.
4. According to the generally accepted state of medical knowledge, comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria according to Chapter 5, Section 6, paragraph 3 VerfO:

On 1. Metformin, sulphonureas, and insulin (human insulin, insulin analogues) are authorised for the mono- and the combination therapy. Marketing authorisations for mono- as well as for the combination therapy also exist for other antidiabetics, among other things alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (gliptine), glinide, SGLT-2 inhibitors (gliflozine) and incretin mimetics.

On 2. A non-drug treatment is not deemed applicable as a comparator therapy in this therapeutic indication.

On 3. The following resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V exist in the therapeutic indication type 2 diabetes mellitus in adults:

- Linagliptin (resolution of 21 February 2013: An additional benefit is deemed not to have been proven; for the combination with metformin, the additional benefit is not proven; resolution of 16 May 2013 (new therapeutic indication): An additional benefit is deemed not to have been proven),
- Dapagliflozin (resolution of 6 June 2013: An additional benefit is not proven; resolution of 21 June 2018 (reassessment based on new scientific knowledge related exclusively to the dual combination therapy with metformin): An additional benefit is not proven),
- Lixisenatide (resolution of 5 September 2013: An additional benefit is not proven; for the combination with oral anti-diabetic drugs, the additional benefit is deemed not to have been proven),
- Saxagliptin/metformin (resolution of 1 October 2013: An additional benefit is not proven),

- Vildagliptin (resolution of 1 October 2013: An additional benefit is not proven; resolution of 21 May 2015. An additional benefit is not proven),
- Vildagliptin/metformin (resolution of 1 October 2013: An additional benefit is not proven),
- Dapagliflozin/metformin (resolution of 7 August 2014: An additional benefit is not proven; resolution of 21 June 2018 (reassessment based on new scientific knowledge): An additional benefit is not proven),
- Canagliflozin (resolution of 4 September 2014: An additional benefit is not proven),
- Insulin degludec (resolution of 16 October 2014: An additional benefit is not proven; resolution of 4 December 2014 (new therapeutic indication): An additional benefit is deemed not to have been proven), resolution of 20 August 2015 (new therapeutic indication): An additional benefit is not proven)
- Canagliflozin/metformin (resolution of 5 February 2015: An additional benefit is not proven),
- Albiglutide (resolution of 19 March 2015: Evidence of a slight additional benefit for the combination with metformin; for other treatment regimens, the additional benefit is not proven).
- Dulaglutide (resolution of 16 July 2015: Indication of a small additional benefit for the combination with insulin (with or without oral anti-diabetic drug); otherwise, the additional benefit is not proven).
- Insulin degludec/liraglutide (resolution of 15 October 2015: An additional benefit is not proven; resolution of 4 February 2016 (new therapeutic indication): An additional benefit is not proven),
- Empagliflozin (resolution of 1 September 2016: For patients with manifest cardiovascular disease in combination with further medication for the treatment of cardiovascular risk factors, indication for a considerable additional benefit for the combination with one or several hypoglycaemic agents; for patients without manifest cardiovascular disease, indication for a small additional benefit for the combination with metformin; for all other patient groups, the additional benefit is not proven),
- Empagliflozin/metformin (resolution of 1 September 2016: An additional benefit is not proven),
- Saxagliptin (resolution of 15 December 2016: An additional benefit is not proven),
- Saxagliptin/metformin (resolution of 15 December 2016: An additional benefit is not proven, resolution of 1 February 2018 (new therapeutic indication): An additional benefit is not proven),
- Sitagliptin (resolution of 15 December 2016: Indication for a small additional benefit for the combination with metformin; for all further patient groups, the additional benefit is not proven; resolution of 22 March 2019 (new benefit assessment after expiry of deadline related exclusively to the dual combination combination therapy with metformin): indication for a small additional benefit)
- Sitagliptin/metformin (resolution of 15 December 2016: An additional benefit is not proven),
- Insulin glargin/lixisenatide (resolution of 16 August 2018: An additional benefit is not proven)
- Ertugliflozin/sitagliptin (resolution of 1 November 2018: An additional benefit is not proven)

– Semaglutide (resolution of 2 May 2019: For patients with manifest cardiovascular disease in combination with further medication for the treatment of cardiovascular risk factors, indication for a small additional benefit for the combination with one or several hypoglycaemic agents; for all other patient groups, the additional benefit is not proven).

On 4. It is assumed that insulin therapy is indicated for patients who are eligible for insulin degludec. The therapy situation "if metformin is unsuitable because of an incompatibility or contraindication" or "if metformin alone does not control the blood sugar level" is not considered in the benefit assessment, because insulin administration is generally not indicated in this therapeutic situation. Only the therapy situations in which an insulin therapy is indicated are considered. In addition, it is assumed that a pharmacotherapy is started only after failure of a single basis therapy (e.g. non-drug measures such as diet and movement) and is always carried out in combination with this.

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

Against the background of the proven benefit by influencing patient-relevant endpoints such as subsequent micro- or macrovascular complications, in accordance with the generally accepted state of medical knowledge, metformin and insulin are to be regarded as appropriate therapies in the therapeutic indication.

Consequently, the combination of metformin and human insulin after failure of at least two hypoglycaemic agents (apart from insulin) constitutes a standard therapy in the therapeutic indication.

In addition, the resolution on empagliflozin is based inter alia on data of the EMPA-REG-Outcome Study. Based on the EMPA-REG Outcome Study, empagliflozin in combination with human insulin is designated as part of the appropriate comparator therapy for patients with type 2 diabetes mellitus with manifest cardiovascular disease in combination with further medication for the treatment of cardiovascular risk factors[6] with regard to cardiovascular endpoints. A manifest cardiovascular disease in this regard was operationalised in accordance with inclusion criteria of the EMPA-REG Outcome Study as at least one of the following conditions: confirmed myocardial infarction, clinically-relevant coronary one-vessel disease with ≥ 50% stenosis, coronary multi-vessel disease, unstable angina pectoris with angiographic evidence of a cardiac disorder, ischaemic or haemorrhagic stroke, or peripheral arterial occlusive disease with clinically relevant ischaemia; see study protocol, Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–28. DOI: 10.1056/ NEJMoa1504720.

In addition, for liraglutide, the Rapid Report of the IQWiG on the cardiovascular long-term study LEADER is available. Based on these positive study results in cardiovascular endpoints, the G-BA concluded that liraglutide in addition to at least one other hypoglycaemic agent for patients with type 2 diabetes mellitus with manifest cardiovascular disease and further medication for the treatment of cardiovascular risk factors[6] is to be regarded as appropriate. A manifest cardiovascular disease was

[3] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352(9131): 854–865.
[4] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359(15):1577–1589.
[5] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131): 837–853
[6] In particular anti-hypertensive drugs, anticoagulants, and/or lipid reducers.

operationalised in this regard in accordance with inclusion criteria of the LEADER study as at least one of the following conditions: confirmed myocardial infarction, confirmed stroke or transient ischaemic attack, clinically relevant arterial occlusive disease or revascularisation, coronary heart disease, confirmed unstable angina pectoris, chronic renal insufficiency (eGFR ≤ 60 ml/min/1.73 m^2) or chronic cardiac insufficiency (NYHA class II or III), see study protocol, Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375: 311–322. DOI: 10.1056/NEJMoa1603827.

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

There has previously been a lack of long-term safety data on the further authorised active ingredients or groups of active ingredients in the therapeutic indication; these are therefore not taken into account as appropriate comparator therapy in the current assessment procedure.

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

On patient group "a)" *(Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar)*: a multiple combination with three or more hypoglycemic agents is critically discussed because of its poor controllability and increased risk of drug interactions and side effects. An insulin therapy in combination with metformin, empagliflozin[2] or with liraglutide[2] is thus indicated in this therapy situation. If metformin, empagliflozin[2], and liraglutide[2] are incompatible or contraindicated in accordance with the product information or are not sufficiently effective because of an advanced type 2 diabetes mellitus and a combination with insulin is not deemed applicable, human insulin alone is the appropriate comparator therapy.

According to the state of medical knowledge, in the antidiabetic therapy situation of patient group "b)" *(Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar),* the optimisation of the human insulin regimen (possibly + metformin or empagliflozin[2] or liraglutide[2]) is designated as an appropriate comparator therapy. The optimisation of the insulin therapy in this regard should be carried out in the form of a conventional insulin therapy (premixed insulin) or an intensified conventional insulin therapy, taking into account the patient's individual life situation. In the course of an intensified conventional therapy (ICT), the administration of an additional hypoglycaemic agent is not regularly considered to be indicated.

It is assumed that for the treatment of co-morbidities in patients with type 2 diabetes mellitus (e.g. hypertonia, dyslipoproteinemias, and coronary artery disease) an individual patient-based treatment of the respective co-morbidities corresponding to the state of medical knowledge, in particular through antihypertensive drugs, anticoagulants and/or lipid reducers, taking into account the specific characteristics of type 2 diabetes mellitus, will be carried out.

For insulin analogues, according to the generally acknowledged level of medical knowledge, there is neither an advantage nor a disadvantage compared to human insulin; however, long-term data with advantages concerning hard endpoints on insulin analogues is available. In the benefit assessment, evidence from studies in which insulin analogues were used are also taken into account if the transferability of the results from studies with human insulin analogues is established. The marketing authorisation status of the insulin analogues must be taken into account. Study results must be examined for possible effect modifications resulting from the type of insulins

used if the studies were carried out with both human insulin and insulin analogues. However, in the cost comparison, the treatment costs for human insulin must be taken into account because this was designated as an appropriate comparator therapy.

The findings set out in Appendix XII for this purpose do not restrict the scope for treatment required for fulfilment of the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

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

In the mono- or combination therapy

a) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

   An additional benefit is not proven.

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

   An additional benefit is not proven.

Justification:

DEVOTE study

For the new benefit assessment because of new scientific knowledge of the active ingredient insulin degludec in the mono- and combination therapy, the pharmaceutical manufacturer in its dossier submits among other thing the DEVOTE study.

Because of the design of the DEVOTE study, the study population includes patients who are to be allocated to both patient group a) and patient group b). There are no separate evaluations for the relevant patient populations a) and b) according to the specifications of the comparator therapies defined by the G-BA. The documents submitted subsequently in connection with the statement procedure were also not suitable for differentiating between the patient groups. An evaluation of the DEVOTE study for an assessment of insulin degludec can therefore only be carried out for all patients of both patient groups a) and b).

The patients enrolled in the DEVOTE study had a manifest cardiovascular disease[7] in addition to the insufficiently controlled type 2 diabetes mellitus. In addition to a "standard therapy", they each received the study medication in the intervention or comparator arm. A standard therapy was defined as a background therapy to the treatment of type 2 diabetes mellitus and other cardiovascular risks in accordance with the local standard.

The study included patients with different pre-treatments of antidiabetic therapy, including the following patient groups:

- Patients without insulin pre-treatment
- Patients with a pre-treatment with basal insulin

[7] in the present case, manifest cardiovascular disease is defined based on the DEVOTE study (see study protocol N Engl J Med. 2017; 377(8):723–732. doi: 10.1056/NEJMoa1615692) and approximately summarised as ≥ 50 years with at least a cardiovascular disease (previous heart attack; stroke or transitory ischaemic attack, revascularisation, > 50% stenosis, previous symptomatic cardiac disorders or unstable angina, asymptomatic cardiac ischaemia, chronic heart failure (NYHA class II-III) or chronic renal failure) or ≥ 60 years with at least one risk factor for cardiovascular diseases (microalbuminuria or proteinuria, high blood pressure and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction or ankle brachial pressure index < 0.9)

- Patients with a pre-treatment with bolus insulin
- Patients with a pre-treatment with basal and bolus insulin (including treatment with premixed insulins).

The DEVOTE study is a randomised, active-controlled, and double blind two-arm study, which was carried out in multiple centres in Africa, Asia, Europe, North America, and South America. In the DEVOTE study, adult parents with type 2 diabetes mellitus and a manifest cardiovascular disease or with at least one risk factor for a cardiovascular disease were enrolled.
In patients from 50 years old, a manifest cardiovascular disease with at least one of the following criteria exist: previous heart attack, stroke or transitory ischaemic attack, revascularisation, > 50% stenosis, and previous symptomatic cardiac disorders or unstable angina, asymptomatic cardiac ischaemia, chronic heart failure (NYHA[8] class II-III), or chronic renal failure.
In patients from 60 years old, at least one risk factor for a cardiovascular disease had to exist if at least one of the following conditions was fulfilled: Microalbuminuria or proteinuria, high blood pressure and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or ankle brachial pressure index < 0.9. Approx. 85% of all patients had a proven cardiovascular disease; in the remaining 15%, there was at least one risk factor for it[7].

Regarding the antidiabetic therapy, the study participants had to receive at least one or more oral or injectable anti-diabetics at the start of the study. In accordance with the inclusion criteria, patients with a HbA1c value ≥ 7.0% (or a HbA1c value < 7.0% if a pre-treatment with ≥ 20 units basal insulin per day occurred) were to be enrolled. At the start of the study, the average HbA1c value was 8.4%.

In total, 7637 patients were randomised at a ratio of 1:1 in the treatment arm insulin degludec ± bolus insulin + standard therapy (N = 3818) and insulin glargin ± bolus insulin + standard therapy (N = 3819). Apart from insulin, all anti-diabetic therapies already existing before the inclusion of the study were retained with unchanged dosage.

An insulin therapy existing before the study inclusion was discontinued at the start of the study and changed to the respective study medication (insulin degludec in the intervention arm and insulin glargin in the comparator arm). For the study participants who did not yet receive any insulin therapy at enrolment, the respective study medication (insulin degludec or insulin glargin) and an insulin regimen were restarted.

In the DEVOTE study, a target value-focused therapy was carried out exclusively based on fasting plasma glucose values (FPG). The dose of the study drug in both study arms should be titrated to a target value of 4.0 to 5.0 mmol/l (71 to 90 mg/dl) using the FPG values. Alternatively, a target value of 5.0 to 7.0 mmol/l (90 to 125 mg/dl) for certain patients could be determined according to the estimate of a principal investigator if such a stringent blood glucose control was not suitable for these patients. The HbA1c values that allow a statement on the longer-term blood glucose control were not taken into account in the titration decision.

In patients who received a therapy with a bolus insulin (possibly in combination with a basal insulin) upon enrolment, a change from insulin could be carried out at the discretion of the investigator. A titration of the dose of the bolus insulin was likewise performed based on self-measured FPG values, which had to be determined before the respective mealtimes. According to the study protocol, a value of 71 to 126 mg/dl was specified as the therapeutic goal.

An intensification of the anti-diabetic treatment with bolus insulin or other anti-diabetic drugs was allowed as determined by the principal investigator in the course of the study. Adequate therapy of cardiovascular risk factors was also planned in both treatment arms. To ensure a

[8] NYHA: New York Heart Association

treatment in accordance with regional guideline recommendations, any accompanying medication required (according to the doctor's assessment) was to be used.

The primary endpoint of the study was the time until the occurrence of one of the following events of the combined MACE endpoint: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The duration of the study was planned to be event-driven until 633 study participants reached the primary combined endpoint. It was assumed that this would be achieved after approx. 5 years.

Before inclusion, about 16% of patients were not insulin-adjusted. A anti-diabetic therapy with insulin existed in 84% of the patients; this occurred in accordance with different therapy strategies. Of these, around 38% of the patients had an insulin therapy (which included only basal insulin) at the start of the study. In 46% of the patients, the anti-diabetic therapy consisted of a basal bolus insulin therapy at the start of the study. In the course of the study, approx. 38% of the patients had a basal insulin therapy. Approx. 62% received a basal bolus insulin therapy.

Suitability of the study for the benefit assessment

After examination of the data, the study shows methodical limitations in different aspects:

Target value-based titration based on the fasting plasma glucose values:

The target values of 4.0 to 5.0 mmol/l (71 to 90 mg/dl) recommended in the study protocol or 5.0 to 7.0 mmol/l (90 to 125 mg/dl) based on the estimate of the investigator are below the intervals of 100 to 125 mg/dl for the fasting plasma glucose values[9] recommended as a benchmark for the therapy of type 2 diabetes mellitus in the last valid National Clinical Guideline. In particular, patient-individual target values for blood glucose control are recommended for the patients with manifest cardiovascular disease or with at least one risk factor for cardiovascular disease and medically justified in accordance with guidelines, the desired therapeutic goal in the study (especially the lower interval of 71 to 90 mg/dl) is classified as too stringent. In accordance with the information provided by the pharmaceutical company at the oral hearing, the titration target of 71 to 90 mg/dl was sought for most of the study participants. It is uncertain for which proportion of these patients a strict near-normal blood glucose control would have been desirable or to what extent the target value for blood glucose control would have been at the upper limit of the target corridor. In addition, from the point of view of the G-BA, not only the FPG value but also the HbA1c value should be taken into account for the titration decision because the latter allows statements on the long-term blood glucose control. This approach is also recommended by the clinical experts.

Implementation of the appropriate comparator therapy

The DEVOTE study investigated insulin degludec in mono- and combination therapy in adults with diabetes mellitus type 2 and manifest cardiovascular disease with regard to the question of cardiovascular safety in comparison to other insulin analogues.

Although the comparison with insulin glargin includes an insulin analogue, which was not explicitly named as part of the appropriate comparator therapy, it is nevertheless accepted as suitable comparator taking into account the current data basis.

Because of the study design, (additional administration of insulin degludec/insulin glargin for the already existing antidiabetic therapy/change of the insulin therapy to these insulin analogues) in addition to the anti-diabetic active ingredients determined as appropriate comparator therapy by the G-BA, further active ingredients were used in combination therapy. Thus, in both treatment arms, considerable proportions of patients with sulphonylureas (approx. 29%) or DPP-IV inhibitors (approx. 12%) was treated in addition to

[9] German Medical Association (BÄK), German National Association of Statutory Health Insurance Physicians (KBV), Association of the Scientific Medical Societies (AWMF). National health care directive of type 2 diabetes – long version , 1st edition. Version 4. 2013, last amended: November 2014.

the insulin therapy. Neither sulphonylureas nor DPP-IV inhibitors are covered by the appropriate comparator therapy in combination with the insulin therapy. In addition, it is unclear for which percentage of the patients the selected therapy strategy corresponded to an adequate therapy adaptation. For example, there is a lack of detailed data on the line of inquiry of patient group b), who did not have any sufficient blood glucose control with their previous insulin therapy at the start of the study and experienced an optimisation of the human insulin regimen during the study. The pharmaceutical entrepreneur did not submit this data either in the dossier or as part of the written statements procedure. Although additional data was transmitted after the oral hearing, this was not adequately processed in accordance with the dossier submission. However, in the overall population in both study arms, the HbA1c value of approx. 8.4% was reduced to 7.5%.

Despite the methodological limitations, because of the duration, size (about 7,600 patients enrolled), and collection of patient-relevant cardiovascular endpoints, the DEVOTE study is considered relevant for the benefit assessment of insulin degludec and allows statements to be made on long-term data, overall survival, cardiovascular safety, and the general safety profile. Hereinafter, the results of the study are assessed for the overall population (i.e also for all patients for patient groups a) and b)).

Results of the DEVOTE study

Mortality and morbidity

Overall mortality/cardiovascular death

There are no significant differences between the treatment groups with respect to overall mortality and the endpoint "cardiovascular death".

Cardiovascular results (MACE)/hospitalisation because of cardiac insufficiency

The combined "Major adverse cardiovascular events (MACE)" includes the endpoints "cardiovascular death", "non-fatal myocardial infarction", and "non-fatal stroke". There are no statistically significant differences between the treatment arms for either the combined endpoint MACE or the individual components. In the endpoint hospitalisation because of cardiac insufficiency, there are also no statistically significant differences.

Quality of life

In the DEVOTE study, no relevant data was collected for an assessment of the health-related quality of life.

Side effects

Serious adverse events (SAE), treatment withdrawal because of AE

For the endpoints SAE and treatment discontinuation because of AE, there are no statistically significant differences between the treatment arms based on the overall rates.

Non-severe, symptomatic, confirmed hypoglycaemias

In the DEVOTE study, no relevant data was collected on the endpoint "non-severe, symptomatic, confirmed hypoglycaemias".

Severe hypoglycaemias

In the DEVOTE study, the endpoint "severe hypoglycaemias" was recorded for different operationalisations. On one hand, "severe hypoglycaemias" were diagnosed; these were documented as SAE. On the other hand "severe hypoglycaemias" were diagnosed; these were either documented as SAE, treated by the administration of intravenous glucose/glucagon, or associated with severe neuroglycopenic symptoms (e.g. altered mental state, unconsciousness, or coma). Depending on operationalisation, different results resulted for the overall population of the DEVOTE study. In the operationalisation of the "severe

hypoglycaemias", which were restricted to the criteria SAE, there was no statistically significant difference between the treatment groups. On the other hand, in the second operationalisation of the "severe hypoglycaemias", which in addition SAE also includes outside help in the form of intravenous administrations of glucose or glucagon as well as severe neuroglycopenic symptoms, there was a statistically significant difference in favour of insulin degludec compared with the control.

However, because of considerable methodical defects in view of a much too stringent titration of the insulin dose in the implementation of the study, these results cannot be fully assessed. The target corridor of the fasting plasma glucose (71 to 90 mg/dl) used in the DEVOTE study was clearly below the intervals of 100 to 125 mg/dl recommended by the last valid National Clinical Guideline[9] for the therapy of type 2 diabetes mellitus. According to the Directive, the specific therapy goal depends on factors such as age, co-morbidity, and the individually agreed therapy goals of the patients[9]. Against the background of the much too low target values for fasting plasma glucose in the DEVOTE study, which were not set individually for each patient, the results for the endpoint "severe hypoglycaemias" are subject to great uncertainties. As a result, it cannot be excluded that the events observed in this endpoint could have been a consequence of the much too strict titration of the insulin dose. In addition, a significant proportion of patients had received sulfonylureas (with hypoglycemic potential) in addition to insulin therapy. This further complicates the interpretation of the results in this endpoint.

Renal dysfunction

For this endpoint, there is no statistically significant difference between the treatment arms.

Additional key points

HbA1c change, change of body weight

For the endpoint "HbA1c change", there is no statistically significant difference between the treatment arms. The endpoints "HbA1c change" and "change of the body weight" constitute surrogate parameters in the treatment of diabetes mellitus and are not patient-relevant *per se*.

Conclusion on the DEVOTE study:

The submitted data of the DEVOTE study address aspects with regard to the overall survival of type 2 diabetes mellitus patients with manifest cardiovascular disease and the general safety profile of insulin degludec in the treatment of this patient group.

Because of the study design and the lack of detailed data on the research questions of the respective patient groups, the DEVOTE study is evaluated jointly for both patient groups a) and b). Concerning the anti-diabetic therapy adaptations carried out, in particular at the start of the study and in the course of the study, it can be assumed that most of the patients have experienced an adequate therapy optimisation.

In the endpoints of the DEVOTE study, no statistically significant differences between the treatment groups was shown apart from the results on the severe hypoglycaemias. In the case of the endpoint "severe hypoglycaemias", there was a positive result for insulin degludec in comparison to the control; however, this was dependent on the nature of the selected operationalisation. Against the background that for most patients, the target values in the titration decision were measured exclusively based on the FPG values (which were far too low and were not determined for individual patients), the results on the endpoint "severe hypoglycaemias" are subject to great uncertainties. As a result, it cannot be excluded that the events observed in this endpoint could have been a consequence of the much too strict titration of the insulin dose.

In the overall picture, no additional benefit can be derived based on the data of the DEVOTE study for the aforementioned reasons.

On the individual treatment regimens

a) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

An additional benefit is not proven.

Justification:

The benefit assessment is based on the studies NN1250-3579 (with the extension study 3579Ext), NN1250-3587, and NN1250-3672 as well as a meta-analytical summary of the studies NN1250-3579, NN1250-3587, and NN1250-3672 (without extension study). In these open, randomised, actively controlled, multi-centre Phase III studies with a duration of 52 weeks (NN1250-3579, further 52 weeks 3579Ext) or 26 weeks (NN1250-3587 and NN1250-3672), the comparison of insulin degludec versus Insulin glargin was investigated in patients wtih type 2 diabetes mellitus.

The study participants in all studies were insulin naive and had not achieved any sufficient blood sugar control with a previous treatment (at least three-months) with metformin alone or in combination with further antibiotics (sulphonylureas, glinide, DPP-IV inhibitors or alpha-glucosidase inhibitors) in unaltered dosage. Furthermore, the patients show a HbA1c value of ≥ 7.0% and ≤ 10%. Apart from metformin (NN1250-3587) or metformin in combination with DPP-IV inhibitors (NN1250-3579 and NN1250-3672), all anti-diabetic drugs were to be discontinued in all studies at the time of the randomisation.

In the NN1250-3579 study, a total 1030 patients were randomised at a ratio of a 3:1 in the study arms insulin degludec (773 patients) and insulin glargin (257 patients), each in combination with metformin ± DPP-IV inhibitor. In the 3579Ext extension study, 551 patients participated in the insulin degludec arm (corresponds to a percentage of 71.3%) and 174 patients in the insulin glargin arm (corresponds to a percentage of 67.7%). The transfer to the extension study occurred without new randomisation.
In the NN1250-3672 study, 460 patients were randomised in the study arms (insulin degludec and insulin glargin, 230 patients in each case) at a ratio of 1:1.
In the NN1250-3587 study, 833 patients were stratified according to region (China/not China) at a ratio of 2:1 in the study arms insulin degludec (555 patients) and insulin glargin (278 patients), each in combination with metformin.

The primary endpoint of all three studies was the change of the HbA1c value from the start of the study to week 52 (NN1250-3579 with the extension study 3579Ext) or to week 26 (NN1250-3587 and NN1250-3672). The patient-relevant secondary endpoints were overall mortality and endpoints for the morbidity, health-related quality of life, and adverse events (AE), including hypoglycaemias.

In the assessment-relevant sub-population, which in the studies included 60 to 67% of the respective overall population, the patients were on average 60 years old. At the start of the study, the patients in both study arms of the three studies had, on average, a HbA1c value of 8.3%; in around 40% of the patients, the value was below 8%. Information on the therapy discontinuation is neither available for the relevant sub-population nor for the overall population of all studies.

During the studies, a titration of the dose of insulin degludec or insulin glargin was performed in the treatment arm; this was based on the self-measured fasting plasma glucose value (FPG). However, instead of the stipulating the therapy goals for each patient, a value of 90 to 125 mg/dl should be reached. The lower value of the target corridor of the fasting plasma glucose value used in the studies was thus below the orientation factor of 100 to 125 mg/dl recommended by the National Clinical Guideline[9] for the therapy of type 2 diabetes mellitus. It is also unclear whether the patients enrolled in the NN1250-3579, NN1250-3587, and NN1250-3672 studies are suitable for a normal control.

Findings of the NN1250-3579, 3579Ext, NN1250-3587, and NN1250-3672 studies

Mortality

Overall mortality

Overall, only a few deaths occurred in the treatment arms of the studies. In the endpoint overall mortality, neither the meta-analysis nor the extension study showed a statistically significant difference between the treatment arms.

Morbidity

Cardiovascular events (MACE)

For the combined endpoint cardiovascular events (MACE), including the single components "cardiovascular death" and "non-fatal stroke", there is no statistically significant difference between the treatment arms for either the meta-analysis or the extension study.

For the endpoint "acute coronary syndrome", the extension study showed a statistically significant effect to the detriment of insulin degludec in combination with metformin. In the meta-analysis, the effect is not statistically significant.

Health status ("daily life" and "mental health" domains of the TRIM-D)

The health status of the patients was recorded with the "daily life" and "mental health" domains of the TRIM-D. In the extension study, the endpoint was not recorded. For this endpoint, no statistically significant difference between the treatment arms was shown in the meta-analysis.

Health-related quality of life

SF-36 – physical component score (PCS) and mental component score (MCS)

For the MCS and PCS of the SF-36, the average alteration at the end of the study compared to the start of the study is considered.

For the MCS, no statistically significant differences between the treatment arms result in the meta-analysis and in the extension study.

For the PCS, there was a statistically significant result for the change compared to baseline in the meta-analysis with a homogeneous data situation. From the standardised mean value difference, estimated with the effect measure Hedges' g ($p < 0.05$), no relevant effect can be derived. Only in the NN1250-3579 study is there a statistically significant effect for the advantage of insulin degludec in combination with metformin; however, this is not relevant when assessed using Hedges' g. In the extension study, there was a statistically significant effect in favour of insulin degludec in combination with metformin; however, when measured by the confidence interval for Hedges' g, it is not clinically relevant. No statistically significant difference between the treatment groups is shown in the studies NN1250-3587 and NN1250-3672. The effects are therefore not commutated.

An additional benefit of insulin degludec versus insulin glargin, each in combination with metformin, is not proven for the category quality of life.

Side effects

Serious adverse events (SAE), treatment discontinuation because of an AE and renal dysfunction.

For the endpoint SAEs, neither the meta-analysis nor the extension study showed a statistically significant difference between the treatment arms.

For the endpoints treatment discontinuation because of an AE and renal dysfunction, neither the meta-analysis nor the extension study showed a statistically significant difference between the treatment arms.

Non-severe symptomatic, confirmed hypoglycaemias

For the non-severe symptomatic, confirmed hypoglycaemias in the operationalisation of a plasma glucose value < 56 mg/dl, the pharmaceutical manufacturer stipulates evaluations of the meta-analysis based on the rate ratio. However, for the assessment of this endpoint, only the evaluation of the relative risk is relevant; this is consistent with the previous assessments in the therapeutic indication.

There is no statistically significant difference between the treatment arms in either the meta-analysis or the extension study.

In addition, the pharmaceutical manufacturer uses additionally separated evaluations according to times of day and derived an additional benefit of insulin degludec for night-time non-severe symptomatic confirmed hypoglycaemias. The relevance of the occurrence of hypoglycaemias at different times of day is currently unclear, in particular against the background that for the overall rate, there are no differences in this endpoint. The results on hypoglycaemias separated according to time of day cannot be conclusively interpreted.

For the endpoint of non-severe symptomatic, confirmed hypoglycaemias, there is thus an additional benefit of insulin degludec versus insulin glargin; however, in combination with metformin, it is not proven for the category quality of life.

Severe hypoglycaemias

In the studies, severe hypoglycaemias were operationalised as hypoglycaemias; these were documented as SAE. For the endpoint severe hypoglycaemias (SAE), neither the meta-analysis nor the extension study showed a statistically significant difference between the treatment groups.

Specific AE

For the endpoint vomiting (PT[10]), there was no statistically significant effect between the treatment arms in the meta-analysis. On the other hand, a statistically significant difference for the benefit of insulin degludec was shown for this endpoint in the extension study.

For the endpoint depressions (PT[10]), there was no statistically significant effect between the treatment arms in the meta-analysis. On the other hand, a statistically significant difference to the detriment of insulin degludec was shown for this endpoint in the extension study.

Additional key points

HbA1c change

For the endpoint "HbA1c change", there was no statistically significant difference between the treatment groups in either the meta-analysis or the extension study.

The endpoint "HbA1c-change" constitutes a surrogate parameter in the treatment of diabetes mellitus and is not relevant to the patient *per se*.

Overall assessment

For the new benefit assessment of insulin degludec in combination with metformin for the treatment of adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin, here metformin) doe not sufficiently control the blood sugar, the NN1250-3587 and NN1250-3672 studies (with a duration of 26 weeks in each case) as well as the NN1250-3579 study (52 weeks) with the extension study 3579Ext (further 52 weeks) were available.

[10] PT: Preferred Term

In the studies, the administration of insulin degludec versus insulin glargin, each in combination with metformin, were compared.

The endpoint categories mortality and health-related quality of life as well as the endpoints cardiovascular events (combined endpoint MACE including the individual components "cardiovascular death" and "non-fatal stroke") and health status (TRIM-D) in the category morbidity do not show any advantages for insulin degludec compared to control for the evaluation-relevant sub-population in both the meta-analysis and the extension study. In the category side effects at the endpoints SAE, treatment discontinuation because of an AE, hypoglycaemias, and renal dysfunctions no positive effects for insulin degludec compared to the control can be derived from the results of the meta-analysis and the extension study.

Statistically significant differences are shown only in the extension study, each to the detriment of insulin degludec in comparison to insulin glargin, for the endpoint acute coronary syndrome in the category morbidity and in the case of the side effects in the PT depression. On the other hand, for the PT vomiting for the side effects in the extension study, there was a statistically significant difference in favour of insulin degludec. The meta-analysis showed no statistically significant differences for these endpoints between the treatment arms. Overall, the distortion potential for all endpoints of the extension study is assessed as too high. As a result, the positive or negative effects observed in this study cannot be unreservedly interpreted in this study.
As part of the Periodic Safety Update Report (PSUR) Assessment Procedure of the EMA, based on the available evidence on insulin degludec, there was no indication for negative effects of insulin degludec on acute coronary syndrome.

Overall, the significance of the current results in relation to the German health care context is subject to considerable uncertainty. Thus, contrary to the recommendations in the Directive, the target values for the fasting plasma glucose in the studies submitted were not determined for each individual patient. These were also under the recommended target corridor for the therapy of type 2 diabetes mellitus[9].

In the overall view, no additional benefit for insulin degludec has been demonstrated in the present patient group compared with the appropriate comparator therapy.

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

An additional benefit is not proven.

Justification:

For the new benefit assessment of insulin degludec, the RCTs NN1250-3582 (including the corresponding extension study NN1250-3667), NN1250-3668, and NN1250-3998 were submitted. Only the study NN1250-3582 with the corresponding extension study is significant for the benefit assessment and is used because only in this study can a sufficient escalation of the anti-diabetic therapy be assumed in the patients included.

The study NN1250-3582 is a two-arm, open Phase III study with a treatment duration of 52 weeks. The patients were able to participate in an extension study (NN1250-3667) for a further 26 weeks after a one-week follow-up observation phase.

Adults with type 2 diabetes mellitus who had received insulin therapy with or without oral anti-diabetics (OAD) for at least three months were included.

The comparison of a combination therapy of insulin degludec and insulin aspart (with or without OAD) with a combination therapy of insulin glargin and insulin aspart (with or without OAD) was investigated. In total,1006 patients in the allotment ratio of 3:1 were randomised to the study arms insulin degludec plus insulin aspart (755 patients) and insulin glargin plus insulin aspart (251 patients), in combination with metformin and/or pioglitazone in each case.

Of these, without new randomisation, 75.0% of the patients from the intervention arm (corresponds to 566 patients) or 76.1% patients from the control arm (corresponds to 191 patients) took part in the extension study NN1250-3667.

For the study, only a sub-population of the patients was relevant. Patients who received metformin only correspond to the line of inquiry if this is done in a dosage that conforms to the approval 1000 to 3000 mg/day). Patients who received pioglitazone are not relevant for the present line of inquiry. The dossier did not contain any evaluations for the relevant sub-population. However, because the vast majority of the enrolled patients is relevant for the present line of inquiry, the data of the entire population is used as an alternative.

During the study, a titration of the dose of insulin degludec or insulin glargin was performed in the treatment arm; this was based on the self-measured fasting plasma glucose value (FPG). However, instead of the stipulating the therapy goals for each patient, a value of 90 to 125 mg/dl should be reached. The lower value of the target corridor of the fasting plasma glucose was thus below the orientation factor of of 100 to 125 mg/dl recommended by the National Clinical Guideline [9] for the therapy of type 2 diabetes mellitus. It is also unclear whether the patients enrolled in the NN1250-3579, NN1250-3587, and NN1250-3672 studies are suitable for a normal control.

Primary endpoint was the HbA1c change from the start of the study to week 52. The patient-relevant secondary endpoints were overall mortality and endpoints for the morbidity, health-related quality, and adverse events.

Findings of the NN1250-3582 studies and the extension study

Mortality

Overall mortality

Overall only a few deaths occurred in the treatment arms. In the endpoint overall mortality, there was no statistically significant difference between the treatment arms.

Morbidity

Cardiovascular events (MACE)

In the endpoint cardiovascular events (MACE) as well as the corresponding individual components cardiovascular death, non-fatal stroke, and acute coronary syndrome, there was no statistically significant difference between the treatment arms.

Health status ("daily life" and "mental health" domains of the TRIM-D)

The health status of the patients was recorded with the "daily life" and "mental health" domains of the TRIM-D. In the principal study NN1250-3582, no statistically significant difference between the treatment arms was shown in each case. In the extension study, the endpoint was not recorded.

Health-related quality of life

SF-36 – physical component score (PCS) and mental component score (MCS)

For the MCS and PCS of the SF-36, the average alteration at the end of the study compared to the start of the study is considered.

There were no statistically significant differences between the treatment arms for either the MCS or the PCS in the principal study NN1250-3582. In the extension study, the endpoint was not included.

Side effects

Serious adverse events (SAE), treatment discontinuation because of an AE and renal dysfunction.

For the endpoint SAE, neither the main study nor the extension study showed a statistically significant difference between the treatment arms.

For the endpoints treatment discontinuation because of an AE and renal dysfunction, neither the main study nor the extension study showed a statistically significant difference between the treatment arms.

Non-severe symptomatic, confirmed hypoglycaemias

For the non-severe symptomatic, confirmed hypoglycaemias in the operalisation of a plasma glucose value < 56 mg/dl, there was no statistically significant difference between the treatment arms in either the principal study or in the extension study.

Severe hypoglycaemias

Severe hypoglycaemias were operationalised as hypoglycaemias; these were documented as SAE. For the endpoint severe hypoglycaemias (SAE), neither the main study nor the extension study showed a statistically significant difference between the treatment groups.

Overall assessment

For the new benefit assessment of insulin degludec in adult type 2 diabetes mellitus patients who, despite diet and movement and the treatment with insulin (with or without another hypoglycaemic agent), did not display any sufficient blood glucose control, the two-arm, open Phase III study NN1250-3582 (with a treatment duration of 52 weeks) as well as the corresponding extension study NN1250-3667 (further 26 weeks) were used. The comparison of insulin degludec versus insulin glargin was investigated, each in combination with insulin aspart (with or without OAD).

Data on various endpoints from the endpoint categories mortality, morbidity, health-related quality of life, and side effects was available. For the endpoints included, there were no statistically significant differences between the treatment arms. Based on this, neither positive nor negative effects for insulin degludec versus insulin glargin were derived.

In the overall view, no additional benefit for insulin degludec has been demonstrated in the present patient group compared with the appropriate comparator therapy.

2.1.4 Brief summary of the assessment

The current assessment is a new benefit assessment of the medicinal product Tresiba® with the active ingredient insulin degludec based on new scientific knowledge, which is indicated in the mono- or combination therapy for the treatment of diabetes mellitus. The new benefit assessment relates exclusively to the therapeutic indication for the treatment of adult patients with type 2 diabetes mellitus.

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with insulin (with or without another hypoglycaemic agent) do not sufficiently control the blood sugar

Patient group a)

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

- Human insulin + metformin *or*

- Human insulin + empagliflozin[2] *or*
- Human insulin + liraglutide[2] *or*
- Human insulin if the particular combination partners in accordance with the product information are incompatible or contraindicated or not sufficiently effective because of an advanced type 2 diabetes mellitus

The randomised, active-controlled, and double blind DEVOTE study was submitted. In this study, type 2 diabetes patients with manifest cardiovascular disease and risk factors for manifest cardiovascular disease were investigated. A comparison with insulin glargin was made.
In the study, a target value-based titration took place based on FPG values. This was not tailored to each individual patient but was rather much too low for most of the patients. For this reason, the results on the endpoint "severe hypoglycaemias", which show a statistically significant difference, are subject to considerable uncertainty. For the other endpoints, no statistically significant differences can be established.

Moreover, the open, randomised and actively controlled studies NN1250-3579 (52 weeks) with the extension study 3579Ext (further 52 weeks) as well as NN1250 3587 and NN1250 3672 (26 weeks in each case) were submitted. These compared insulin degludec and insulin glargin, each in combination with metformin. Overall, for the results of the meta-analysis of the individual studies as well as the extension study, it must be assumed that there are neither advantages not disadvantages for insulin degludec in the endpoints included.

In the overall picture, the additional benefit of insulin degludec compared with the appropriate comparator therapy is not proven for this patient group.

Patient group b)

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

- The optimisation of the human insulin regimen (possibly + metformin *or* empagliflozin[2] *or* liraglutide[2])

The randomised, active-controlled, and double blind DEVOTE study was submitted. In this study, type 2 diabetes patients with manifest cardiovascular disease and risk factors for manifest cardiovascular disease were investigated. A comparison with insulin glargin was made.
In the study, a target value-based titration took place based on FPG values. This was not tailored to each individual patient but was rather much too low for most of the patients. For this reason, the results on the endpoint "severe hypoglycaemias", which show a statistically significant difference, are subject to considerable uncertainty. For the other endpoints, no statistically significant differences can be established.

Moreover, three RCTs were submitted; of these, only the RCT NN1250-3582 (including the corresponding extension study) is relevant. The relevant study had a treatment duration of 52 weeks plus a further 26 weeks in the corresponding extension study. Insulin degludec was compared with insulin glargin. For the endpoints included, there were no statistically significant differences between the treatment arms.

In the overall picture, the additional benefit of insulin degludec compared with the appropriate comparator therapy is not proven for this patient group.

2.2 Number of patients and/or demarcation of the patient groups elibible for treatment

This information on the number of patients concerns the target population in the statutory health insurance.

The data basis concerning the published literature on the current prevalence and incidence of diabetes mellitus in Germany is restricted and heterogeneous despite the significance of the disease. Especially for sub-populations in the therapy cascade of diabetes therapy, there is a lack of valid published data, which is why some patient numbers can only be estimated.

The G-BA takes into account the patient numbers of the corresponding therapy situations indicated for antidiabetic drugs in resolutions already adopted in accordance with Section 35a SGB V, possibly taking into account a range. This takes into account the uncertainties concerning the restricted epidemiological data basis on type 2 diabetes mellitus.

Regarding the percentage of patients with and without manifest cardiovascular disease[7], no valid data is available. This contributes to further uncertainty regarding the patient numbers. Therefore, the resolution includes an indication of patient groups without separate presentations of patient numbers with and without manifest cardiovascular disease[7].

2.3 Requirements for quality-assured application

The requirements of the product information must be taken into account. The European Medicines Agency (EMA) makes the contents of the product information on Tresiba® (active ingredient: Insulin degludec) freely available under the following link (last access: 12. April 2019):
https://www.ema.europa.eu/documents/product-information/stalevo-epar-product-information_de.pdf

2.4 Treatment costs

The treatment costs are based on the data of the product information as well as the data of the German official price list for pharmaceuticals [Lauer-Taxe®] (Last revised: 15. April 2019).

Concerning the usage and consumption, the average annual consumption was calculated by indicating the number of tablets or individual doses. The daily doses recommended in the product information were used as the calculation basis and, if required, corresponding margins were formed. The separate description of possibly required titration phases was dispensed with because the antidiabetic therapy is a continuous long-term therapy, and the titration is performed individually for each patient.

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

For metformin, initial dosages of 500 mg or 850 mg two to three times daily are recommended, but dose increases to up to 3,000 mg metformin daily are possible; the overall dose is generally allocated to 2–3 doses. The cost representation is therefore based on a potency of 1,000 mg metformin/tablet.

For empagliflozin, an initial dosage of 10 mg once daily as combination therapy with other hypoglycaemic agents including insulin is recommended. If there is insufficient metabolic control, the dose can be increased to 25 mg once daily. Therefore, both potencies are taken into account for the cost representation.

The daily initial dose of liraglutide is 0.6 mg; after one week, this is increased to 1.2 mg. According to the product information, patients can possibly benefit from a further increase of the dose from 1.2 mg to 1.8 mg. The corresponding dose of liraglutide is injected subcutaneously every day (single-use pen).

For the insulin therapy, a large number of various insulin dosage schemes is possible. In addition, in accordance with the insulin dosage scheme used, the quantity of insulin and the application frequency must be coordinated individually according to the patient's physical

activity and lifestyle. In order to guarantee a comparability of the costs, simplified assumptions have been made for the presentation of the treatment duration and dosage. In the table "Treatment duration", the mode of treatment for human insulin (NPH insulin or premixed insulin) is represented as "1–2 × daily" even if the application frequency can deviate in some patients. According to the product information[11], the average insulin requirement is often 0.5–1.0 I.U. per kg body weight per day. One unit (U) of insulin degludec corresponds to 1 I.U. of human insulin. The basal daily insulin requirement is generally 40–60% of the daily insulin requirement; the remaining requirement is covered through mealtime-dependent bolus insulin. The calculation of bolus insulin consumption is based on three main meals. The calculation of the dose of insulin per day was based on this data.

In principle, the G-BA does not base the calculation of the consumption of weight-dependent medicinal products to be dispensed on indication-specific average weights. Therefore, for the body weight, a mean body weight of 77.0 kg according to the official representative statistic "Microcensus 2017" is assumed[12].

Consequently, weight differences between women and men as well as the fact that body weight in patients with type 2 diabetes mellitus can lie above the mean value of 77.0 kg are not taken into account for the cost calculation.

Treatment duration:

Designation of the therapy	Mode of treatment	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed (patient populations a) and b))				
Insulin degludec	continuously, 1 × daily	365	1	365
possibly human insulin (bolus insulin)	continuously, 3 × daily	365	1	365
possibly + metformin	continuously, 2–3 × daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
Human insulin (NPH insulin)	continuously, 1–2 × daily	365	1	365
possibly + metformin	continuously, 2–3 × daily	365	1	365
possibly + empagliflozin	continuously, 1 × daily	365	1	365

[11] Product information on Insuman® Basal, last revised: April 2018.

[12] German Federal Office for Statistics, Wiesbaden, 2 August 2018. Microcensus 2017: Questions on health; body measurements of the population 2017 [online]. [Access: 13 September 2018]. https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Mode of treatment	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
possibly + liraglutide	continuously, 1 × daily	365	1	365
Patient population b)				
<u>Intensified conventional insulin therapy</u> Human insulin (bolus insulin)	continuously, 3 × daily	365	1	365
Human insulin (NPH insulin)	continuously, 1–2 × daily	365	1	365
<u>Conventional insulin therapy</u> Premixed insulin	continuously, 1–2 × daily	365	1	365
possibly + metformin	continuously, 2–3 × daily	365	1	365
possibly + empagliflozin	continuously, 1 × daily	365	1	365
possibly + liraglutide	continuously, 1 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage	Dose/patient/treatment days	Usage and consumption according to potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
Medicinal product to be assessed					
Insulin degludec	0.5 -	38.5 U. -	1 x 38.5 U. -	365	14,052.5 U. -
	1 U. per kg/BW	77 U.	1 × 77 U.		28,105 U.
Insulin degludec (in combination with bolus insulin)	0.2 -	15.4 U. -	1 × 15.4 U.[13] -	365	5,621 U. -
	0.6 U. per kg/BW	46.2 U.	1 × 46.2 U.[4]		16,863 U.
possibly + human insulin (bolus insulin)	0.2 -	15.4 I.U. -	1 × 15.4 I.U.[4] -	365	5,621 I.U. -
	0.6 I.U. per kg/BW	46.2 I.U.	1 × 46.2 I.U.[4] -		16,863 I.U.
possibly + metformin	500 mg -	1,000 mg -	1 × 1,000 mg -	365	365 × 1,000 mg - -
	1,000 mg	3000 mg	3 × 1,000 mg		1095 × 1,000 mg
Appropriate comparator therapy					
Patient population a)					
Human insulin (NPH)	0.5 -	38.5 -	1 × 38.5 I.U. -	365	14,052.5 I.U. -
	1 I.U. per kg/BW	77 I.U.	1 × 77 I.U.		28,105 I.U.
possibly + metformin or	500 mg -	1,000 mg -	1 × 1,000 mg -	365	365 × 1,000 mg -
	1,000 mg	3,000 mg	3 × 1,000 mg		1095 × 1,000 mg
possibly + empagliflozin	10 mg -	10 mg -	1 × 10 mg -	365	365 × 10 mg -

[13] 40–60% of the daily insulin requirement is generally covered through basal insulin: 0.5–1.0 I.U./kg body weight /day; reference: 77 kg body weight ("Microcensus 2017"); in addition, fast-acting insulin (bolus insulin) is given at main mealtimes.

Designation of the therapy	Dosage	Dose/patient/treatment days	Usage and consumption according to potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
or	25 mg	25 mg	1 × 25 mg		365 × 25 mg
possibly + liraglutide	1.2 mg[14] -	1.2 mg -	1 × 1.2 mg -	365	365 × 1.2 mg -
	1.8 mg	1.8 mg	1 × 1.8 mg		365 × 1.8 mg
Patient population b)					
<u>Intensified conventional insulin therapy</u>[13]					
Human insulin (NPH insulin) +	0.2 - 0.6 I.U. per kg/BW	15.4 - 46.2 I.U.	1 × 15.4 - 1 × 46.2 I.U.	365	5,621 I.U. - 16,863 I.U.
Human insulin (bolus insulin)	0.2 - 0.6 I.U. per kg/BW	15.4 - 46.2 I.U.	1 × 15.4 -- 1 × 46.2 I.U.	365	5,621 I.U. - 16,863 I.U.
<u>Conventional insulin therapy</u>					
Premixed insulin	0.5 - 1 I.U. per kg/BW	38.5 - 77 I.U.	1 × 38.5 I.U. - 1 × 77 I.U.	365	14,052.5 I.U. - 28,105 I.U.
possibly + metformin	500 mg -	1,000 mg -	1 × 1,000 mg -	365	365 × 1,000 mg -
	1,000 mg	3,000 mg	3 × 1,000 mg		1095 × 1,000 mg
possibly + empagliflozin	10 mg -	10 mg -	1 × 10 mg -	365	365 × 10 mg -
	25 mg	25 mg	1 × 25 mg		365 × 25 mg

[14] In accordance with the product information, each single-use contains 18 mg of liraglutide in 3 ml of solution; this corresponds to 10–15 single doses. Packages with 2, 5, and 10 single-use pens are available.

Designation of the therapy	Dosage	Dose/patient/treatment days	Usage and consumption according to potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
possibly + liraglutide	1.2 mg[16] -	1.2 mg -	1 × 1.2 mg -	365	365 × 1.2 mg -
	1.8 mg	1.8 mg	1 × 1.8 mg		365 × 1.8 mg

Costs:

Costs of the medicinal products:

The calculation of the treatment costs for the active ingredients metformin, gilbenclamide and glimepiride, human insulin and premixed insulin was based on the fixed amount in each case.

For the calculation of drug costs, the required number of packs according to potency was first determined on the basis of consumption. The medicinal product costs were calculated with the calculated number of required packs, based on the costs per packs, after deduction of the statutory discount. The medicinal product costs were charged approximately both on the basis of the pharmacy sales price level as well as minus the legally prescribed discounts in accordance with Section 130a SGB V (paragraph 1, 1a, 3a) and in accordance with Section 130 paragraph 1 SGB V for the sake of better comparability.

In the case of a conventional insulin therapy, the costs were based on the costs for premixed insulin (i.e. a human insulin preparation in a certain premixing ratio of 30% normal insulin to 70% basal insulin).

Designation of the therapy	Package size	Costs (pharmacy sales price)	Sales discount according to Section 130 SGB V	Sales discount according to Section 130a SGB V	Costs after deduction of statuatory discounts
Medicinal product to be assessed					
Insulin degludec	3000 U.	€ 103.54	€ 1.77	€ 5.12	€ 96.65
possibly + metformin[15] 1,000 mg	180 FTA	€ 18.78	€ 1.77	€ 0.62	€ 16.39
possibly + human insulin (bolus insulin)[15]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Appropriate comparator therapy					
Empagliflozin 10 mg	100 FTA	€ 192.34	€ 1.77	€ 10.04	€ 180.53

[15] Fixed amount

Designation of the therapy	Package size	Costs (pharmacy sales price)	Sales discount according to Section 130 SGB V	Sales discount according to Section 130a SGB V	Costs after deduction of statuatory discounts
Empagliflozin 25 mg	100 FTA	€ 192.34	€ 1.77	€ 10.04	€ 180.53
Human insulin (bolus insulin)[15]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Human insulin (NPH insulin)[15]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Liraglutide 18 mg	100 – 150 SD	€ 570.64	€ 1.77	€ 30.99	€ 537.88
possibly + metformin[15] 1,000 mg	180 FTA	€ 18.78	€ 1.77	€ 0.62	€ 16.39
Premixed insulin[15]	3,000 I.U.	€ 89.64	€ 1.77	€ 6.22	€ 81.65
Abbreviations: U = Units; SD = Single Doses; FTA = Film Tablets, I.U. = International Units; TAB = Tablets					

Lauer-Taxe last revised: 15. April 2019

Costs for additional SHI services required.

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

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

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additional SHI services required had to be taken into account.

Other SHI services:

None

3. Bureaucratic costs

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

4. Process sequence

The pharmaceutical manufacturer with the letter of 4. Juli 2017, received on 5. Juli 2017, a consultation in accordance with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) among other things on the question of the appropriate comparator therapy was requested. In its meeting on 12. September 2017, the

Subcommittee on Medicinal Products determined the appropriate comparator therapy. The consultation meeting took place on 21. September 2017.

Because of new scientific knowledge, the appropriate comparator therapy was reviewed, and the Subcommittee on Medicinal Products determined the appropriate comparator therapy once again in its meeting on 24 October 2017.

On 28. November 2018, the pharmaceutical manufacturer submitted a dossier for the benefit assessment of Insulin degludec to the G-BA in due time in accordance with Chapter 5, Section 8 paragraph 1 number 5 VerfO.

The G-BA commissioned the IQWiG with the letter of 29. November 2018 in conjunction with the resolution of the G-BA of 1 August 2011 on the commissioning of the IQWiG concerning the assessment of the benefit of the medicinal product with new active ingredients pursuant to Section 35a SGB V to carry out the assessment of the dossier on the active ingredient Insulin degludec.

The dossier assessment by the IQWiG was submitted to the G-BA on 27. Februar 2019 together with the publication on 1. März 2019 on the websites of the G-BA, thus initiating the written statement procedure. The deadline for submitting written statements was 22. März 2019.

The oral hearing was held on 8. April 2019.

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 provider, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participated in the meetings.

The evaluation of the written statements received and the oral hearing was discussed at the meeting of the subcommittee on 7. Mai 2019, and the proposed resolution was approved.

At its meeting on 16. Mai 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Meeting	Date	Subject of the resolution
Subcommittee Medicinal product	12. September 2017	Determination of the appropriate comparator therapy
Working group Section 35a	5 October 2017 18 October 2017	Review of the appropriate comparator therapy
Subcommittee Medicinal product	24. Oktober 2017	Change of the appropriate comparator therapy
Working group Section 35a	2. April 2019	Information on statements received; preparation of the oral hearing
Subcommittee Medicinal product	8. April 2019	Conduct of the oral hearing Possibly: commissioning of the IQWiG to carry out an additional assessment of documents
Working group Section 35a	16. April 2019 30. April 2019	Discussion on the dossier assessments by the IQWiG and the evaluation of the statement

		procedure
Subcommittee Medicinal product	7. Mai 2019	Final discussion of the proposed resolution
Plenum	16. Mai 2019	Adoption of a resolution on the amendment of Appendix XII AM-RL

Berlin, 16. Mai 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof Hecken