Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Dulaglutide (Renewed Benefit Assessment Because of New Scientific Knowledge in Accordance with Section 13 (Type 2 Diabetes Mellitus))

of 16 July 2020

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient dulaglutide (Trulicity®) was first placed on the (German) market on 1 February 2015. At its session on 16 July 2015, the G-BA passed a resolution on the benefit assessment of dulaglutide in accordance with Section 35a SGB V. The G-BA prompted a new benefit assessment in accordance with 35a, paragraph 1 SGB V 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 dulaglutide at the request of its members in the resolution of 18 July 2019. The renewed benefit assessment was prompted based on new scientific knowledge from the completed REWIND (NCT01394952) study.

The relevant date for the first placing on the market of the active ingredient dulaglutide in accordance with Chapter 5, Section 8, paragraph 1, number 6 of the Rules of Procedure of the G-BA (VerfO) is 1 February 2020. The pharmaceutical company 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 31 January 2020.

The G-BA 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 4 May 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of dulaglutide compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of dulaglutide.

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 of dulaglutide (Trulicity®) in accordance with the product information (Last revised October 2019)

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

– as monotherapy when metformin is considered inappropriate due to intolerance or contraindications

– in addition to other medicinal products for the treatment of diabetes.

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance

Appropriate comparator therapy:

- Sulphonylurea (glibenclamide or glimepiride)

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar

Appropriate comparator therapy:

- Metformin + sulphonylurea (glibenclamide or glimepiride) or
- Metformin + empagliflozin or
- Metformin + liraglutide

  liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents[2]

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

[2] for the operationalisation, 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

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

  empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents[3]

d) 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

d1) in patients without renal insufficiency

Appropriate comparator therapy:

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

  empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents[3]

d2) in patients with moderate or severe renal insufficiency in accordance with chronic kidney disease CKD stage 3 and 4 defined by an eGFR value < 60 to ≥ 15 ml/min/1.73 m^2

Appropriate comparator therapy:

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

  liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents[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 according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

[3] 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

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

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

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication:

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

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

On 3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.

- Linagliptin (resolution of 21 February 2013: An additional benefit is 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),
- Lixisenatide (resolution of 5 September 2013: An additional benefit is not proven; for the combination with oral anti-diabetics, 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),
- 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; resolution of 16 May 2019 (reassessment because of new scientific knowledge related exclusively to the treatment of adult patients with type 2 diabetes mellitus): An additional benefit is not proven).

- Canagliflozin/metformin (resolution of 5 February 2015: An additional benefit is not proven),
- Albiglutide (resolution of 19 March 2015: Indication for a minor additional benefit for the combination with metformin; for other treatment regimens, the additional benefit is not proven),
- Insulin degludec/liraglutide (resolution of 15 October 2015: An additional benefit is not proven; resolution of 4 February 2016 (new therapeutic indication): An additional benefit is not proven).
- Empagliflozin (resolution of 1 September 2016: 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, hint for a minor 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: Hint for a minor 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 therapy with metformin): Hint for a minor additional benefit).
- Sitagliptin/metformin (resolution of 15 December 2016: An additional benefit is not proven).
- Insulin glargine/lixisenatide (resolution of 16 August 2018: An additional benefit is not proven).
- 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, hint for a minor additional benefit for the combination with one or several hypoglycaemic agents; for all other patient groups, the additional benefit is not proven).
- Empagliflozin/linagliptin (resolution of 22 November 2019: An additional benefit is not proven).
- Dapagliflozin (resolution of 19 December 2019: Hint for a minor additional benefit in combination therapy of dapagliflozin with one or more hypoglycaemic agents and only for patients at high cardiovascular risk receiving further medication for the treatment of cardiovascular risk factors; for all other patient groups, the additional benefit is not proven).
- Dapagliflozin/metformin (resolution of 19 December 2019: Hint for a minor additional benefit only for patients at high cardiovascular risk receiving further medication for the treatment of cardiovascular risk factors; for all other patient groups, the additional benefit is not proven).

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

Metformin is a first-choice oral anti-diabetic agent with proven reduction of overall mortality and heart attack risk[4,5]. For human insulin, a reduction of diabetes-related microvascular complications is proven[6].

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

For empagliflozin in the dual combination with metformin, positive study results are available from Study 1245.28 and the EMPA-REG-Outcome Study regarding cardiovascular endpoints of empagliflozin for patients with type 2 diabetes mellitus exclusively with manifest cardiovascular disease. For the dual combination of empagliflozin with metformin, a hint for a minor additional benefit was found for all patients with type 2 diabetes mellitus compared with the appropriate comparator therapy metformin in combination with sulphonylurea (glimepiride). Furthermore, based on the EMPA-REG-Outcome Study, there was a hint for a considerable additional benefit of empagliflozin in combination with additional medication for the treatment of cardiovascular risk factors for the combination with one or more hypoglycaemic agents for patients with manifest cardiovascular disease. Based on these results, empagliflozin was therefore only named as part of the appropriate comparator therapy for patients with manifest cardiovascular disease. 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[7] is to be regarded as appropriate. A manifest cardiovascular disease was operationalised in this regard in accordance with inclusion criteria of the LEADER study

[4] 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.
[5] 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.
[6] 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
[7] In particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents.

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: 311322. DOI: 10.1056/NEJMoa1603827. Furthermore, in the LEADER study, for patients with renal insufficiency with an eGFR < 60 ml/min/1.73 m^2, there were benefits for overall mortality, stroke, and the combined endpoint MACE.

There has previously been a lack of long-term safety data on the further approved 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.

It is assumed that anti-diabetic therapy is initially started with metformin monotherapy. If metformin is not suitable because of contraindications/intolerance, a sulphonylurea should be used.

In patients with renal dysfunction with a glomerular filtration rate GFR < 60 to 30 ml/min, metformin can be administered in accordance with the product information taking into account the corresponding maximum daily dose.

For patient group “b)” *(Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar)*, human insulin may be used as a therapeutic option in individual cases in patients for whom metformin is intolerable or contraindicated in accordance with the product information. Because this is a small patient group overall, no separate appropriate comparator therapy is determined.

On patient group “c)” *(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 hypoglycaemic active ingredients is critically discussed because of its poor controllability and an increased risk for medicinal products interactions and side effects so that in this therapy situation, insulin therapy may be indicated in combination with metformin, empagliflozin, or liraglutide. If metformin, empagliflozin, and liraglutide 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.

In the anti-diabetic therapy situation of patient group “d)” *(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 administration of an additional blood hypoglycaemic agent is not regularly considered to be indicated in the context of an ICT.

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 anti-hypertensive drugs,

anticoagulants and/or lipid-lowering agents, taking into account the specific characteristics of type 2 diabetes mellitus, will be carried out.

For insulin analogues, according to the generally recognised state of medical knowledge, there are neither advantages nor disadvantages compared with 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.

Although insulin glargine is an insulin analogue that 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.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of dulaglutide is assessed as follows.

a) Adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance

   An additional benefit is not proven.

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar

   An additional benefit is not proven.

c) 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.

d) 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

   d1) in patients without renal insufficiency

      Hint for a minor additional benefit.

   d2) in patients with moderate or severe renal insufficiency in accordance with chronic kidney disease CKD stage 3 and 4 defined by an eGFR value < 60 to ≥ 15 ml/min/1.73 m^2

      Hint for a minor additional benefit.

Justification:

<u>Cross-patient group aspects</u>

The REWIND study was presented for the renewed benefit assessment of dulaglutide according to Section 35a SGB V in patients with type 2 diabetes mellitus and high cardiovascular risk.

Patients with different previous treatments were included in the study. The study medication in the intervention or comparator arm was given in addition to a “standard therapy” of type 2 diabetes mellitus and other cardiovascular risk factors and comorbidities. Because of the design of the REWIND study, the total population includes patients with different comparative therapies. These cannot be classified into the different patient populations in accordance with the specifications of the G-BA for the corresponding patient groups as well as the respective comparison therapy options defined. The REWIND study can therefore be assessed only across all patient groups together.

REWIND study

The REWIND study is a randomised, double blind, placebo controlled two-arm study, which was carried out in multiple centres in Africa, Asia, Australia, Europe, and North and South America. The REWIND study included adult patients aged ≥ 50 years with type 2 diabetes mellitus and an HbA1c value ≤ 9.5%; a lower limit for the HbA1c value was not defined. The patients showed a high cardiovascular risk, which was defined as follows: Patients with a minimum age of 50 years had to have a **manifest cardiovascular disease** (e.g. history of myocardial infarction or stroke).
Patients with a minimum age of 55 years had to have a **sub-clinical manifest cardiovascular disease** (e.g. documented vascular stenosis of > 50% in coronary vessels, carotid artery, or lower extremity arteries or an estimated glomerular filtration rate (eGFR) permanently < 60 ml/min/1.73 m^2).
Patients with a minimum age of 60 years had to have at least two **risk factors for cardiovascular disease** (e.g. tobacco consumption or hypertension).

At the start of study, 31% of the study participants had a manifest cardiovascular disease. At least 20% had an eGFR value < 60 to ≥ 30 ml/min/1.73 m^2.

The patient characteristics were balanced between the treatment groups: the patients were 66 years old on average; 36% of the study participants can be assigned to the region Europe. At the start of study, the average HbA1c value was 7.3%, and systolic blood pressure was 137 mmHg.

A total of 9901 patients were randomised to the treatment arms dulaglutide 1.5 mg (N = 4949) or placebo (N = 4952) at a ratio of 1:1. Dulaglutide or placebo was administered in addition to the existing anti-diabetic treatment and cardiovascular background therapy. Almost all patients (95%) received anti-diabetic therapy at the start of study; approx. 24% were treated with insulin (possibly in combination with oral anti-diabetics), approx. 81% with metformin, and approx. 46% with sulphonylurea. More than 90% of the study participants were given at least one cardiovascular concomitant treatment with anti-hypertensive drugs, lipid-lowering agents, and/or antithrombotic medication at the start of study.

In order to achieve the HbA1c target values, it was possible to adjust the anti-diabetic background therapy at the investigator's discretion and according to local guidelines and standards. According to the study protocol, if the HbA1c target values were not achieved and/or severe hyperglycaemia occurred, additional therapeutic measures were recommended. At the discretion of the investigator, it was possible to implement these only from month 3 after randomisation unless earlier intervention was indicated. Treatment with other GLP-1 receptor agonists and DPP-4 inhibitors was not allowed during the study. Regarding the treatment of cardiovascular risk factors, the investigator's assessment was that both arms were to be treated in accordance with the national standard.

The study duration was planned to be event-driven until at least 1,200 patients with a confirmed serious cardiovascular event (MACE) were recorded and designed for a treatment period of 7 years. The median observation period was 5.2 years. Patients who discontinued the study medication prematurely after randomisation were monitored until the end of study.

The primary endpoint of the study was the combined endpoint MACE, consisting of cardiovascular death, non-lethal myocardial infarction, and non-lethal stroke. Further patient-relevant endpoints in the mortality, morbidity, and adverse events category were recorded. Endpoints of the health-related quality of life category were not collected.

Suitability of the study for the benefit assessment

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

Implementation of the appropriate comparator therapy

Instead of an individual presentation of results for all questions of the G-BA presented under 2.1.2 *Appropriate comparator therapy*, the pharmaceutical company presents in its dossier, inter alia, the REWIND study for a question it defined regarding the treatment of type 2 diabetes mellitus patients with increased cardiovascular risk with dulaglutide in addition to a standard therapy compared with a standard therapy.

Adult patients with type 2 diabetes mellitus and increased cardiovascular risk represent a sub-population of patients covered by the therapeutic indication of dulaglutide. The additional benefit is to be demonstrated for all patient groups compared with the specific appropriate comparator therapy as specified by the G-BA. The pharmaceutical company does not provide evaluations that cover all patient groups.

Irrespective of this, the REWIND study is also not entirely suitable for the comparison with a standard therapy intended by the pharmaceutical company. Against the background that the patients included had a high cardiovascular risk or manifest cardiovascular disease, it is questionable whether the standard anti-diabetic therapy performed in the study corresponds to a recommended one according to the current state of medical knowledge for the treatment of diabetes mellitus. Especially in patients with type 2 diabetes mellitus and manifest cardiovascular disease, treatment with liraglutide or empagliflozin has been shown to have a positive effect in preventing death. In accordance with the current guidelines,[8] the active ingredients liraglutide and empagliflozin, both of which were determined by the G-BA to be part of the appropriate comparator therapy, particularly in patients with manifest cardiovascular disease, are expressly recommended for patients with a high cardiovascular risk[8] or manifest cardiovascular disease. Liraglutide (GLP-1 receptor agonist, GLP-1-RA) was not allowed at any time in the REWIND study. Because of this limitation, only 75 patients (1.5%) in the comparator arm had received GLP-1-RA, including liraglutide, after the start of study. Although treatment with empagliflozin was allowed within the study, only 488 patients (9.9%) in the control group were treated with SGLT-2 inhibitors, including empagliflozin, after the start of study. Especially against the background of the very low use of liraglutide and empagliflozin (total < 10%), the anti-diabetic therapy carried out in the study does not seem appropriate. The results of the REWIND study can therefore not be transferred to the German healthcare context with sufficient certainty and cannot be interpreted with sufficient validity.

Further uncertainties result from the therapy with dulaglutide performed in the study. Because, in accordance with the product information, dulaglutide is indicated only as an adjuvant to diet and exercise in inadequately controlled type 2 diabetes mellitus, and due to the fact that more than half of the patients had an HbA1c value below 7.5% at the start of study, it is not possible to assess conclusively whether the majority of patients would have required an escalation of anti-diabetic therapy at all.

In addition, when considering glycaemic thresholds at different observation points, it can be deduced that in more than 40% of the patients in the comparator arm, who, with an HbA1c value > 7.5% at the start of study, would probably have needed an escalation of the blood glucose-lowering therapy, no equivalent blood glucose control was achieved compared with the dulaglutide arm. Thus, the proportion of patients with an HbA1c value ≥ 7.5% was significantly higher in the comparator arm than in the dulaglutide arm at both month 3 (47.5%

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

vs 17.7%) and month 12 (46.7% vs 22.4%). Because of identical targets and existing escalation possibilities of the anti-diabetic concomitant therapy in both treatment arms, a corresponding comparable reduction of the HbA1c value between the intervention with dulaglutide and the control, or at least an extensive approximation within the first year of study, would have been expected. The reasons for the lower reduction of HbA1c values in the comparator arm compared with the dulaglutide arm are not evident. For example, from the adjustments made to anti-diabetic therapy in the course of the study, it cannot be deduced that the escalation possibilities would have been 100% exhausted. It is not clear to what extent the insulin strategy was optimised in patients treated with insulin.

Concomitant treatment of cardiovascular risk factors and comorbidities

The data on blood pressure over the course of the study also indicate that the care with regard to cardiovascular risk factors and cardiovascular diseases was also inadequate and not implemented according to the guidelines in the study protocol. Over the course of the study, there were noticeable differences in systolic blood pressure between treatment groups in favour of dulaglutide even though the study design would have expected a comparable blood pressure between treatment groups.

Summary

Particularly considering the further development of anti-diabetic therapy and taking into account the current guideline recommendations[8], which recommend the use of liraglutide or empagliflozin in patients with manifest cardiovascular disease or a high cardiovascular risk, it would have been expected that the patients would have been treated to a higher extent with liraglutide or empagliflozin as part of the standard therapy. Because these active ingredients, which were also determined as an appropriate comparator therapy by the G-BA, were only used to a very small extent, the study results cannot be fully transferred to the German healthcare context. Nevertheless, because of the number of patients included, the patient-relevant endpoints investigated (especially with respect to cardiovascular events and overall mortality), and the median observation period of 5.2 years (median), the study is assessed overall for the early benefit assessment according to Section 35a SGB V.

On the results of the REWIND study:

Extent and probability of the additional benefit

Mortality and morbidity

Overall mortality/cardiovascular mortality

There are no statistically significant differences between treatment groups with respect to overall mortality and the endpoints “cardiovascular death”, “lethal myocardial infarction”, or “lethal stroke”.

Combined endpoint MACE

The combined endpoint “Major adverse cardiovascular event (MACE)” includes the endpoints “cardiovascular death”, “non-lethal myocardial infarction”, and “non-lethal stroke”. The combined endpoint MACE shows statistically significant differences in favour of dulaglutide. When considering the individual components, the endpoint “non-lethal stroke” shows a statistically significant advantage for dulaglutide. For the other components, there are no statistically significant differences between the treatment arms.

Hospitalisation because of cardiac insufficiency or urgent visit because of cardiac insufficiency

For this endpoint, an urgent visit was defined as an urgent, unscheduled visit to a doctor or emergency room with clinical signs and symptoms of cardiac insufficiency and the need for additional or intensified therapy. There were no statistically significant differences between the treatment arms.

Chronic renal replacement therapy

The endpoint “chronic renal replacement therapy” was assessed in patients undergoing dialysis or kidney transplantation. There were no statistically significant differences between the treatment arms.

Persistent deterioration of renal function

The endpoint “persistent deterioration of renal function” was operationalised as persistent doubling of serum creatinine compared with baseline (in two consecutive measurements) and persistent eGFR ≤ 45 ml/min/1.73 m^2 (in two consecutive calculations). There is a statistically significant advantage for dulaglutide compared with the control.

Combined endpoint diabetic retinopathy

The endpoint diabetic retinopathy consisted of the individual components “diabetic retinopathy requiring laser therapy”, “diabetic retinopathy requiring vitrectomy”, and “diabetic retinopathy requiring anti-VEGF therapy”. There are no statistically significant differences between the treatment arms in either the combined endpoint or the respective individual components.

Quality of life

In the REWIND study, no endpoints in the quality of life category were collected.

Side effects

Total rates

Serious adverse events and discontinuation because of adverse events

No statements on statistical significance can be made regarding the total rate of adverse events (AE). For the total rate of the serious adverse events (SAE), there are no statistically significant differences between the treatment arms. For the endpoint “Discontinuation because of AE”, there is a statistically significant disadvantage for dulaglutide compared with placebo.

Specific adverse events

Severe hypoglycaemias and acute pancreatitis

For the endpoints “severe hypoglycaemias” and “acute pancreatitis”, there are no statistically significant differences between the treatment arms.

Gastrointestinal disorders

In the endpoint “gastrointestinal disorders” (SOC), in this case for the PT “nausea” and “diarrhoea”, there are statistically significant differences to the disadvantage of dulaglutide.

Additional endpoints

HbA1c change

The change in HbA1c from start of study to month 60 showed a statistically significant difference to the benefit of dulaglutide. The endpoint “HbA1c” is a surrogate parameter and not per se patient-relevant.

Body weight

The change in body weight from start of study to month 60 showed a statistically significant difference to the benefit of dulaglutide. The endpoint “body weight” is a surrogate parameter and not per se patient-relevant.

Overall assessment

For patient groups b), c), and d), in each case in adult patients with type 2 diabetes mellitus and high cardiovascular risk

The REWIND study was presented for a renewed benefit assessment according to Section 35a SGB V based on new scientific findings of dulaglutide as monotherapy or in combination with other anti-diabetics for the treatment of inadequately controlled type 2 diabetes mellitus in adults as a supplement to diet and exercise. Based on the data presented, statements can only be made for patients with type 2 diabetes mellitus with a high cardiovascular risk. For patients without high cardiovascular risk, with the exception of patient group d1, there are no suitable studies available for comparison with the appropriate comparator therapy.

The study investigated dulaglutide versus placebo, in each case, in addition to a standard therapy defined as a patient-individual background therapy for the treatment of type 2 diabetes mellitus and other cardiovascular risk factors and comorbidities in accordance with the national standard. For a monotherapy with dulaglutide no meaningful data can be derived overall (see section on the individual treatment regimens below).

Overall, the REWIND study has methodological limitations. For the implementation of the appropriate comparator therapy, uncertainties arise with respect to the therapy options with liraglutide or empagliflozin, both determined as appropriate comparator therapy by the G-BA. In the study, liraglutide and empagliflozin were used only to a limited extent even though both active ingredients demonstrated a positive effect in preventing deaths and, in accordance with the guidelines[8], are explicitly recommended for patients with manifest cardiovascular disease or high cardiovascular risk. Thus, it cannot be assumed with sufficient certainty that the patients in the comparator arm have received adequate anti-diabetic treatment. Against this background, the study results cannot be transferred to the German healthcare context with sufficient certainty. In addition, it cannot be ruled out that, for some of the patients, there may not have been a need to escalate at the start of study.

However, despite the methodological limitations identified, the study is assessed overall for the early benefit assessment according to Section 35a SGB V because of the number of patients included, the median observation period of 5.2 years, and the patient-relevant endpoints investigated, particularly with regard to cardiovascular events and overall mortality.

In the mortality category, there was no statistically significant differences between the treatment groups.

In the morbidity category for the combined endpoint “MACE” (consisting of the individual components cardiovascular death, non-lethal myocardial infarction, and non-lethal stroke), in the individual component “non-lethal stroke”, and in the endpoint “persistent deterioration of renal function”, there is a statistically significant advantage for dulaglutide compared with the control.
For the other individual components “cardiovascular death” and “non-lethal myocardial infarction” of the endpoint MACE, and for the endpoints “hospitalisation because of cardiac insufficiency”, “chronic renal replacement therapy”, and “diabetic retinopathy” there are no statistically significant differences between the treatment groups.

Endpoints for the quality of life category were not collected in the study.

In the side effects category, dulaglutide showed a statistically significant disadvantage compared with the control arm in the endpoints “discontinuation because of adverse events”

and “gastrointestinal disorders (SOC)” in the PT “nausea” and “diarrhoea”. For the total rate of SAE, there are no statistically significant differences between the treatment arms.

Taking into account the no more than minor positive effects in the morbidity categories as well as the negative effects in the side effects and considering the aforementioned methodological limitations of the REWIND study, no additional benefit is derived in the overall view.

On the individual treatment regimens:

Patient group a)

Patient group a) includes adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance.

An additional benefit is not proven.

No study relevant for the benefit assessment was presented compared with the appropriate comparator therapy (sulphonylurea: glibenclamide or glimepiride) that would have been appropriate to evaluate the additional benefit of dulaglutide monotherapy for the treatment of adult patients with inadequately controlled type 2 diabetes mellitus in addition to diet and exercise if the use of metformin is not indicated because of intolerance or contraindications.

In the REWIND study presented for the assessment of the additional benefit (see cross-patient group aspects above), only 5.4% of patients were treated with dulaglutide without further anti-diabetic medication. It is also unclear to what extent these patients or the proportion of patients for whom the approval criterion “metformin intolerance or contraindication, as an adjunct to diet and exercise” was considered. Treatment with dulaglutide was also administered at twice the recommended dose as specified in the product information for dulaglutide monotherapy. Consequently, no meaningful data can be derived from this study to assess the additional benefit of dulaglutide in the (anti-diabetic) monotherapy in patients with type 2 diabetes mellitus if diet and exercise alone do not adequately control blood glucose and the use of metformin is considered unsuitable because of intolerance. The REWIND study is therefore not suitable for assessing the additional benefit of dulaglutide monotherapy.

Patient group b)

Patient group b) includes adult patients with type 2 diabetes mellitus, in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar.

An additional benefit is not proven.

The AWARD-6 study was presented to compare dulaglutide versus liraglutide, each in combination with metformin. For the renewed benefit assessment, the pharmaceutical company uses an evaluation for a sub-population of patients with manifest cardiovascular disease from the AWARD 6 study.

AWARD-6 study

The AWARD-6 study is a two-arm, randomised, actively controlled, open-label study with a treatment duration of 26 weeks. Included were adults with type 2 diabetes mellitus in whom blood glucose was insufficiently controlled despite an appropriate diet and exercise and pre-treatment with metformin. In accordance with the inclusion criteria, the HbA1c value had to be ≥ 7.0% and ≤ 10.0%.

The AWARD-6 study examines the comparison of dulaglutide with liraglutide. In the study, a total of 599 patients were randomised to treatments with dulaglutide or liraglutide, each in combination with metformin, at a ratio of 1:1.

The primary endpoint of the study was the change in HbA1c levels from baseline after 26 weeks of treatment. Other endpoints were overall mortality as well as endpoints on morbidity and adverse events.

Since in this patient group, the G-BA has determined liraglutide as an appropriate comparator therapy only for patients with manifest cardiovascular disease[9], the pharmaceutical company forms a sub-population of patients with manifest cardiovascular disease in accordance with the inclusion criteria of the REWIND study (see above). The sub-population of the AWARD-6 study presented by the pharmaceutical company is considered to be a sufficient approximation to the G-BA requirement regarding the determination of liraglutide as an appropriate comparator therapy only in patients with manifest cardiovascular disease. In addition, the information on the concomitant medication of the patients in the study suggests that the comprehensive use of anti-hypertensive drugs, lipid-lowering agents, or anticoagulants for the treatment of cardiovascular risk factors was ensured.

For the sub-population, the data of 44 patients (20 in the intervention arm and 24 in the comparator arm) are evaluated.

On the findings of the AWARD-6 study:

Extent and probability of the additional benefit

Mortality

No deaths occurred.

Morbidity

For morbidity category endpoints, there are no usable data for the sub-population.

Quality of life

In the AWARD-6 study, no endpoints in the quality of life category were collected.

Side effects

No statements on statistical significance can be made regarding the total rate of AE.

For the total rate of SAE as well as discontinuation because of AE, there are no statistically significant differences between the treatment arms.

For the other endpoints non-severe, symptomatic, confirmed hypoglycaemia and severe hypoglycaemia, no usable data are available for the sub-population.

Overall assessment

Patient group b)

Patient group b) includes adult patients with type 2 diabetes mellitus, in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar. To assess the additional benefit of dulaglutide compared

[9]For the operationalisation, 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

with liraglutide, each in combination with metformin, the pharmaceutical company presents a sub-population of the AWARD-6 study involving patients with manifest cardiovascular disease.

Adult patients with type 2 diabetes mellitus and manifest cardiovascular disease are only a sub-group of patient group b). Because there are no studies available for patients with type 2 diabetes mellitus without manifest cardiovascular disease, no statements can be made about the additional benefit of dulaglutide for patients without manifest cardiovascular disease.

Based on the AWARD-6 study in patients with manifest cardiovascular disease, there are no statistically significant differences between the treatment arms and no usable data for the relevant sub-population. Therefore, no statements on the additional benefit of dulaglutide in this patient group can be made on this basis.

For the assessment of the REWIND study, reference is made to the aforementioned comments on cross-patient group aspects.

Patient group c)

Patient group c) includes 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.

The REWIND study in which patients with type 2 diabetes mellitus and a high cardiovascular risk are examined was submitted.

Adult patients with type 2 diabetes mellitus and a high cardiovascular risk are only a sub-group of patient group c). Because there are no studies available for patients with type 2 diabetes mellitus without high cardiovascular risk, no statements can be made about the additional benefit of dulaglutide for patients without high cardiovascular risk in patient group c).

For the assessment of the REWIND study, reference is made to the aforementioned comments on cross-patient group aspects.

Patient group d)

Patient group d) includes adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar.

For the assessment of the REWIND study in patients with a high cardiovascular risk, reference is made to the aforementioned comments on cross-patient group aspects.

d1) In patients without renal insufficiency

Hint for a minor additional benefit.

According to the generally accepted procedure in evidence-based medicine, for the present renewed benefit assessment of dulaglutide, all studies in the approved therapeutic indication of dulaglutide, including the relevant AWARD-4 study in the patient population d1), would have to be included. The AWARD-4 study was not submitted in the dossier of the pharmaceutical company. With modules 1 and 4 from the first dossier of dulaglutide of 2 February 2015, which were subsequently submitted within the framework of the written statement procedure, as well as the new analyses on the cardiovascular endpoints, the pharmaceutical company at least formally complies with the obligation to submit the entire body of evidence. Because the

pharmaceutical company has not addressed all the criticisms presented in the justification for the resolution of 16 July 2015 and in the IQWiG report on the benefit assessment A15-07 of 29 April 2015, the additional evaluations are not considered.

Because on one hand, no meta-analytical evaluations of the AWARD-4 and AWARD-7 studies (see below) can be carried out and because it is not assumed that further data cut-offs from the AWARD-4 study are available, the results from the resolution of 16 July 2015 will exceptionally be considered for the present assessment.

The directly comparative AWARD-4 study is used to demonstrate an additional benefit of dulaglutide in combination with insulin lispro compared with insulin glargine in combination with insulin lispro.

AWARD-4 study

The AWARD-4 study is a randomised, actively controlled pivotal study (Phase III) with a treatment phase of 52 weeks. The study was double-blind for the different doses of the test intervention and open for the comparative intervention. Included were adult patients with type 2 diabetes mellitus who showed inadequate blood glucose control under optimised and stable insulin dosage with conventional insulin therapy alone or in combination with oral anti-diabetic therapy together with diet and exercise. In accordance with the inclusion criteria, the AWARD-4 study included patients with an HbA1c value ≥ 7.0% and ≤ 11.0%. At the start of study, the mean HbA1c baseline was 8.5% in both treatment arms and below 8.5% in about 55% of patients.

A total of 884 patients were randomised to the three treatment arms at a ratio of 1:1:1. The patients received either dulaglutide 0.75 mg weekly (293 patients), dulaglutide 1.5 mg weekly (295 patients), or the long-acting insulin analogue insulin glargine (296 patients), each in combination with the short-acting insulin lispro (bolus insulin) with or without metformin (≥ 1,500 mg/day). For the assessment of the additional benefit of dulaglutide in combination with insulin, the results of the dulaglutide arm at the dose of 1.5 mg/week were used because this is the recommended weekly dose according to the product information.

After the screening phase, the study comprised a 9-week initiation phase, a 52-week treatment phase, and a 4-week follow-up phase.

The primary endpoint of the study was the change of the HbA1c value after 26 weeks.

In the course of the study, insulin therapy with insulin glargine and insulin lispro was optimised according to defined algorithms. The insulin glargine dose was adjusted based on the three previous fasting plasma glucose values. A target value between 71 and 99 mg/dl was sought. The lispro insulin dose for administration before breakfast, lunch, and supper was also adjusted (the same for all treatment groups) according to a pre-specified algorithm based on the last three fasting plasma glucose values before lunch, supper, and bedtime. The target values were between 71 and 100 mg/dl (before lunch, supper) and between 71 and 130 mg/dl (before bedtime). Thus, in both treatment arms, a target value-oriented insulin therapy was carried out with the aim of a blood glucose adjustment close to the norm.

<u>On the findings of the AWARD-4 study:</u>

<u>Extent and probability of the additional benefit</u>

For the endpoints included in the assessment, evaluations for several time periods were sometimes available. For the present assessment, the evaluation for each endpoint was based on the evaluation over the longest available time period (even after administration of the emergency medication) so that for most endpoints, evaluations were included in the assessment at 52 weeks.

Mortality and morbidity

Overall mortality

In the AWARD-4 study, deaths were recorded only as safety endpoints. Overall, there were few deaths in the treatment arms. There was no statistically significant difference in overall mortality between treatment groups.

Cardiovascular morbidity

The cardiovascular morbidity endpoint was operationalised by the pharmaceutical company as the number of patients with at least one adjudicated cardiovascular event consisting of lethal cardiovascular and non-lethal[10] cardiovascular events (SOC for cardiac events). The pharmaceutical company presents the overall event rates but not the results of the individual components. Because of the lack of individual components of the combined endpoint, this endpoint is not assessed.

Health status (EQ-5D-VAS)

Data on health status were surveyed using the EQ-5D VAS (visual analogue scale of the Euro-Qol-5D questionnaire). The direct comparison showed no statistically significant difference between dulaglutide and insulin glargine, both in combination with insulin lispro with or without metformin.

Quality of life

For the survey instruments used in the AWARD-4 study (EQ-5D, APPADL/IW-SP, and LBSS), there was no adequate validation for the target population. Thus, there are no usable data on quality of life in the AWARD-4 study.

Side effects

Total rates

Severe adverse events (SAE)

For the endpoint SAE (patients with ≥ 1 SAE), there was a statistically significant treatment difference in favour of dulaglutide + insulin lispro with or without metformin compared with insulin glargine + insulin lispro with or without metformin for the period up to week 52. Events occurred across all organ classes without accumulation in one area. Hypoglycaemia was also included in the SAE endpoint; however, there is no evidence that the result was different from hypoglycaemia with or without the inclusion of events.

Discontinuation because of adverse events (AE)

Compared with insulin glargine, treatment with dulaglutide, each in combination with insulin lispro with or without metformin, leads to a statistically significant greater proportion of patients with discontinuation because of AE for the period up to week 52. Hypoglycaemia was also recorded under the endpoint discontinuation because of AE. However, the result remains statistically significant even after the deduction of patients with hypoglycaemia. Nausea and dyspepsia from the SOC “gastrointestinal disorders” were the most common reasons for discontinuation because of AE in the dulaglutide arm. In the control arm, neither nausea nor dyspepsia were the cause of therapy discontinuation.

Specific adverse events

Symptomatic hypoglycaemias

[10] Myocardial infarction, hospitalisation because of unstable angina pectoris, coronary intervention (coronary bypass surgery or percutaneous coronary intervention).

The results for the endpoints on hypoglycaemia were considered; the operationalisation of this includes both symptomatology and confirmation by measurement of blood glucose levels (< 54 mg/dl or ≤ 70 mg/dl). For the endpoints on symptomatic hypoglycaemia with blood glucose limits of < 54 md/dl and ≤ 70 mg/dl, there was no statistically significant difference between the treatment groups for the period up to week 52.

Severe hypoglycaemias

In the operationalisation of severe hypoglycaemia, the pharmaceutical company includes the criterion of external aid in the dossier in accordance with the definition of the American Diabetes Association (ADA) used in the study report as operationalisation. However, external help alone is not a sufficiently reliable criterion for severe hypoglycaemia because this would also be the case for the enrichment of oral carbohydrates, for example. It cannot then be ruled out that "non-severe" hypoglycaemias are also included among the severe hypoglycaemias. More specific would be operationalisations that limit outside help to medical aid (e.g. the administration of glucose or glucagon) or the detection of hypoglycaemia that was life-threatening or resulted in hospitalisation. The present operationalisation does not ensure that only severe hypoglycaemia is detected. There are therefore no usable data for this endpoint.

Gastrointestinal disorders

For the endpoint gastrointestinal disorders (SOC), there was a statistically significant difference between the treatment groups to the disadvantage of dulaglutide compared with insulin glargine (each in combination with insulin lispro with or without metformin).

Nausea, diarrhoea, dyspepsia, loss of appetite, and vomiting

Gastrointestinal events were considered on the basis of the *preferred terms (PT) nausea, diarrhoea, loss of appetite, dyspepsia, and vomiting*. For the endpoints nausea, vomiting, dyspepsia and, loss of appetite, there was a statistically significant difference to the disadvantage of dulaglutide compared with insulin glargine. According to the study report of the AWARD-4 study, the gastrointestinal side effects are predominantly assessed as mild to moderate[11]by the patients.

Pancreatitis

All cases of acute pancreatitis, possibly acute pancreatitis, asymptomatic pancreatic enzyme elevation, and serious AE (abdominal pain) were evaluated and adjudicated by an independent committee. In neither of the two relevant treatment arms did pancreatitis occur.

Reaction at the injection site

Reactions at the injection site were recorded as further specific side effects. These were classified using several MedDRA terms and included (local) events that were classified with the term "injection site reaction" or that were classified by the investigators as reactions at the injection site (e.g. rash, itching, redness, or pain). There are no treatment differences between the relevant treatment arms.

Additional endpoints

HbA1c change

The change in HbA1c from start of study to week 52 showed a statistically significant difference to the benefit of dulaglutide. The endpoint "HbA1c" is a surrogate parameter and not per se patient-relevant.

[11] In accordance with study report M4A_H9X_MC_GBDD_Studienbericht, time point 52 weeks.

Body weight

There is a statistically significant difference in the change in body weight to the advantage of dulaglutide. The endpoint “body weight” is a surrogate parameter and not per se patient-relevant.

Overall assessment

Patient group d1)

Patient group d1) includes adult patients with type 2 diabetes mellitus without renal insufficiency in whom diet and movement and the treatment with one other hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar. The AWARD-4 study is used to assess the additional benefit of dulaglutide in combination with insulin lispro (with or without metformin).

The AWARD-4 study is a randomised, actively controlled study that included patients with type 2 diabetes mellitus who were inadequately controlled under conventional insulin therapy alone or in combination with oral anti-diabetics. The administration of dulaglutide in combination with insulin lispro was compared with an open therapy with insulin glargine in combination with insulin lispro. The results for the endpoints were predominantly assessed at 52 weeks of treatment.

In the mortality category for the endpoint overall mortality and in the morbidity category for the health status endpoint determined using the EQ-5D VAS, there are no significant differences between the treatment groups. For the combined cardiovascular morbidity endpoint, no statements on statistical significance can be made because of the missing presentation of the individual components.

No data are available in the health-related quality of life category.

In the side effects category, there is a statistically significant difference in the prevention of severe adverse events in favour of dulaglutide in combination with insulin lispro compared with the control arm. In contrast, there are statistically significant disadvantages for dulaglutide compared with control for discontinuation because of to adverse events and in the endpoint gastrointestinal disorders (SOC), especially nausea, diarrhoea, dyspepsia, loss of appetite, and vomiting (PT).

In the overall view of the results on mortality, morbidity, and side effects, there is one positive and several negative effects for dulaglutide. In weighing up, the negative effects for the endpoints discontinuation because of AE, gastrointestinal disorders, nausea, diarrhoea, vomiting, dyspepsia, and loss of appetite do not entirely question the benefit of dulaglutide for SAE. Nevertheless, they lead to a weakening of the benefit so that overall there is a minor additional benefit from dulaglutide in combination with insulin lispro (with or without metformin) compared with insulin glargine in combination with insulin lispro.

Reliability of data (probability of additional benefit)

The reliability of data is classified in the “hint” category. Because only the results of a single randomised controlled trial (AWARD-4) are available for deriving an additional benefit of dulaglutide in combination with insulin lispro (with or without metformin) compared with insulin glargine in combination with insulin lispro, a classification in the “proof” category is not justified.

The risk of bias at the study level was rated as low for the AWARD-4 study.

At the endpoint level, the lack of blinding of the test intervention versus the active reference substance leads to a risk of bias potential rated as high for subjectively reported endpoints. Accordingly, the risk of bias for the following endpoints was assessed as high, thus deviating from the assessment of the pharmaceutical company: EQ-5D-VAS, discontinuation because of AE, symptomatic hypoglycaemia (blood sugar < 54 mg/dl and ≤ 70 mg/dl), nausea,

diarrhoea, vomiting, loss of appetite, pancreatitis, gastrointestinal disorders (SOC), dyspepsia, and reactions at the injection site.

In contrast, there is a low risk of bias for the endpoint SAE. The reliability of data for this endpoint is thus based on the assumption that there is an indication of less harm under treatment with dulaglutide in combination with insulin lispro (with or without metformin) compared with insulin glargine in combination with insulin lispro.

In the overall view, the AWARD-4 study shows a low risk of bias at the study level in connection with a mostly high risk of bias at the endpoint level because of a lack of blinding of the test intervention versus the active reference substance. In the overall statement on additional benefit, a maximum of one hint for an additional benefit is assumed.

d2) In patients with moderate or severe renal insufficiency in accordance with chronic kidney disease CKD stage 3 and 4 defined by an eGFR value < 60 to ≥ 15 ml/min/1.73 m^2

Hint for a minor additional benefit.

For the assessment of the additional benefit of dulaglutide in patients with type 2 diabetes mellitus with moderate or severe renal failure who are not adequately controlled by pre-treatment with insulin with or without an oral anti-diabetic, the AWARD-7 study was presented to compare dulaglutide with insulin glargine, each in combination with insulin lispro.

AWARD-7 study

The AWARD-7 study is a three-arm, randomised, actively controlled, open-label Phase III study with a treatment duration of 52 weeks. The study included adults with type 2 diabetes mellitus and moderate to severe chronic renal disease (Stage 3 and 4) in accordance with the guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NFK KDOQI). The stages were defined as an estimated glomerular filtration rate (eGFR) of < 60 to ≥ 15 ml/min/1.73 m^2. The study investigated the comparison of a combination therapy of dulaglutide and insulin lispro (each in two different doses of dulaglutide) with a combination therapy of insulin glargine and insulin lispro in patients who had an HbA1c value between ≥ 7.5% and ≤ 10.5% at the start of study.

A total of 577 patients were randomised to the treatment arms dulaglutide 0.75 mg per week, dulaglutide 1.5 mg per week, and insulin glargine, each in combination with insulin lispro at a ratio of 1:1:1. For the present assessment, only the approval-relevant treatment arm with 1.5 mg dulaglutide per week is used. Patients were stratified according to the severity of the chronic renal disease (stage 3a, 3b, or 4).

During the study, both the dose of insulin glargine in the control arm and the dose of insulin lispro administered prandially three times daily in both study arms were titrated using the three-day mean of the fasting plasma glucose (FPG). Therapy goals were not set for each individual patient. Instead, an average glucose value of < 154 mg/dl was to be achieved. Insulin glargine was titrated to a uniform FPG value of 100 to 150 mg/dl and insulin lispro to a uniform plasma glucose value of 120 to 180 mg/dl. The study's target value of < 154 mg/dl (8.6 mmol/l) or HbA1c < 7% corresponds to the target value recommended by the NFK KDOQI guideline for diabetes and chronic kidney disease as a guide. The therapy regime administered in the control arm of the study corresponded to an intensified conventional therapy (ICT).

The patient characteristics were largely comparable between the treatment arms. The patients had a mean HbA1c value of 8.6% at the start of study.

The primary endpoint of the study was the change in HbA1c levels from baseline after 26 weeks of treatment. Further endpoints were endpoints on mortality, morbidity, and side effects up to 52 weeks of treatment.

On the findings of the AWARD-7 study

Extent and probability of the additional benefit

Mortality and morbidity

Overall mortality

Only a few deaths occurred in the study. For the endpoint overall mortality, there was no statistically significant difference between the treatment arms.

Progression of an end-stage renal disease

The endpoint progression of an end-stage renal disease (ESRD) was operationalised by the following events:

- Chronic renal disease Stage V
- Need for renal replacement therapy *or*
- eGFR < 15 ml/min/1.73 m^2.

For this endpoint, there are no statistically significant differences between the treatment arms.

Quality of life

In the AWARD-7 study, no endpoints in the quality of life category were collected.

Side effects

Total rates

Serious adverse events and discontinuation because of adverse events

No statements on statistical significance can be made regarding the total rate of adverse events (AE). For the total rate of the serious adverse events (SAE), there are no statistically significant differences between the treatment arms. For the endpoint "Discontinuation because of AE", there is a statistically significant disadvantage for dulaglutide compared with the control.

Specific adverse events

Non severe, symptomatic hypoglycaemias

For this endpoint, non-severe symptomatic confirmed hypoglycaemias with a plasma glucose threshold (PG) < 54 mg/dl and ≤ 70 mg/dl were considered. For both PG < 54 mg/dl and PG ≤ 70 mg/dl, there is a statistically significant difference in favour of dulaglutide compared with insulin glargine, both in combination with insulin lispro. In the course of the study, the blood glucose reduction in the intervention arm was comparable to that in the comparator arm.

Severe hypoglycaemias

For the endpoint severe hypoglycaemia, there is a statistically significant advantage of dulaglutide and insulin lispro compared with the control arm.

Gastrointestinal disorders

In the endpoint "gastrointestinal disorders" (SOC), in this case for the PT "nausea" and "diarrhoea", there are statistically significant differences to the disadvantage of dulaglutide.

Acute pancreatitis

In the endpoint "acute pancreatitis", there are no statistically significant differences between the treatment arms.

Additional endpoints

HbA1c change

For the change in the HbA1c value, no statements on statistical significance between the treatment arms can be made. The endpoint “HbA1c” is a surrogate parameter and not per se patient-relevant.

Body weight and body mass index (BMI)

Changes in body weight and BMI each show a statistically significant difference to the advantage of dulaglutide. The endpoints “body weight” and BMI are surrogate parameters and not patient-relevant per se.

Overall assessment

Patient group d2)

Patient group d2) includes adult patients with type 2 diabetes mellitus with moderate or severe renal failure according to chronic kidney disease CKD Stage 3 and 4 – defined by an eGFR value < 60 to ≥ 15 ml/min/1.73 m^2 in which treatment with insulin (with or without another hypoglycaemic agent) in addition to diet and exercise does not sufficiently control blood sugar. The AWARD-7 study was submitted to assess the additional benefit of dulaglutide in combination with insulin lispro (with or without metformin).

The AWARD-7 study is a randomised, actively controlled open-label study in patients with type 2 diabetes mellitus and moderate to severe chronic kidney disease (Stage 3 and 4) in accordance with the guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NFK KDOQI) who, under conventional insulin therapy alone or in combination with oral anti-diabetics, had an HbA1c value between ≥ 7.5% and ≤ 10.5%. The administration of dulaglutide in combination with insulin lispro was compared with an open therapy with insulin glargine in combination with insulin lispro. Data with a 52-week treatment duration are available for the benefit assessment.

In the mortality category for the endpoint overall mortality and in the morbidity category for the endpoint progression to end-stage renal disease, there are no significant differences between the treatment groups.

No data are available in the health-related quality of life category.

In the side effects category, there are statistically significant advantages of dulaglutide compared with insulin glargine (in each case in combination with insulin lispro) in the prevention of non-severe, symptomatic hypoglycaemias (PG ≤ 54 mg/dl as well as supplemental < 70 mg/dl) and severe hypoglycaemias. In contrast, there are statistically significant disadvantages for dulaglutide in the case of discontinuation because of adverse events and in the endpoint gastrointestinal disorders (SOC), in particular the specific adverse events diarrhoea, nausea, and vomiting (PT). There are no statistically significant differences between the treatment arms in the other endpoints for SAE and the endpoint acute pancreatitis.

In the overall view, weighing up the positive and negative effects of dulaglutide, the extent of the additional benefit is rated as low.

Reliability of data (probability of additional benefit)

The AWARD-7 study was submitted to assess the additional benefit of dulaglutide in combination with insulin lispro in adult patients with type 2 diabetes mellitus with moderate or severe renal failure according to chronic kidney disease CKD Stage 3 and 4 – defined by an eGFR value < 60 to ≥ 15 ml/min/1.73 m^2 in which treatment with insulin (with or without another hypoglycaemic agent) in addition to diet and exercise does not sufficiently control blood sugar.

The AWARD-7 study is an open-label study in which dulaglutide was compared with insulin glargine, each in combination with insulin lispro. Because of the open design, the risk of bias of the results of all endpoints included is considered high.

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

2.1.4 Summary of the assessment

The present evaluation is a renewed benefit assessment of the medicinal product Trulicity® containing the active ingredient dulaglutide, which is indicated as monotherapy or in addition to other anti-diabetics for the treatment of inadequately controlled type 2 diabetes mellitus in adult patients as a supplement to diet and exercise.

In the present case, the entire approved therapeutic indication is considered. Four patient groups were distinguished; the last patient group comprised two sub-populations.

a) Adult patients with type 2 diabetes mellitus in whom diet and movement alone do not sufficiently control the blood sugar and for whom the use of metformin is not suitable because of intolerance

b) Adult patients with type 2 diabetes mellitus in whom diet and movement and the treatment with one hypoglycaemic agent (apart from insulin) do not sufficiently control the blood sugar

c) 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

d) 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

d1) in patients without renal insufficiency

d2) in patients with moderate or severe renal insufficiency in accordance with chronic kidney disease CKD stage 3 and 4 defined by an eGFR value < 60 to ≥ 15 ml/min/1.73 m^2

Patient group a)

Sulphonylurea (glibenclamide or glimepiride) was determined as an appropriate comparator therapy by the G-BA.

The randomised, double-blind, placebo-controlled REWIND study in which patients with type 2 diabetes mellitus with an HbA1c value ≤ 9.5% and manifest cardiovascular disease or high cardiovascular risk were examined was presented. The administration of dulaglutide was compared to placebo, in each case in addition to a “standard therapy” of type 2 diabetes mellitus in accordance with the national standard.

In the study, only 5.4% of patients were treated with dulaglutide without further anti-diabetic medication. It is also unclear to what extent these patients or the proportion of patients for whom the approval criterion “metformin intolerance or contraindication, as an adjunct to diet and exercise” was considered. Treatment with dulaglutide was also administered at twice the recommended dose as specified in the product information for dulaglutide monotherapy. In the overall view, no meaningful data can be derived for the assessment of the additional benefit of dulaglutide in (anti-diabetic) monotherapy compared with the appropriate comparator therapy. The additional benefit is not proven.

Patient group b)

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

- Metformin + sulphonylurea (glibenclamide or glimepiride) or
- Metformin + empagliflozin or
- Metformin + liraglutide

Liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents.

The randomised, double-blind, placebo-controlled REWIND study in which patients with type 2 diabetes mellitus with an HbA1c value ≤ 9.5% and manifest cardiovascular disease or high cardiovascular risk were examined was presented. The administration of dulaglutide was compared to placebo, in each case in addition to a “standard therapy” of type 2 diabetes mellitus in accordance with the national standard. The median observation period was 5 years.

In the REWIND study, liraglutide and empagliflozin, which were included in the appropriate comparator therapy, were used only to a limited extent, although both agents are explicitly recommended in the guidelines for patients with manifest cardiovascular disease or high cardiovascular risk because of their proven benefit in preventing death. Against this background, it cannot be assumed with sufficient certainty that the patients in the comparator arm received an adequate anti-diabetic treatment. The study results can therefore not be transferred to the German healthcare context with sufficient certainty. In addition, it cannot be ruled out that, for some of the patients, there may not have been a need to escalate at the start of study. Nevertheless, because of the number of patients included, the patient-relevant endpoints investigated, and the median observation period of about 5 years, the study is assessed overall for the early benefit assessment according to Section 35a SGB V.

In the morbidity category in the combined endpoint “MACE” (consisting of the individual components cardiovascular death, non-lethal myocardial infarction, and non-lethal stroke), in the individual component “non-lethal stroke”, and in the endpoint “persistent deterioration of renal function”, there is a statistically significant advantage for dulaglutide compared with the control. In contrast, dulaglutide shows a statistically significant disadvantage in the side effects category in the endpoints “discontinuation because of adverse events” and “gastrointestinal disorders”, each in the PT “nausea” and “diarrhoea”. For the remaining endpoints, including endpoints of the mortality category (overall mortality, cardiovascular death, lethal myocardial infarction, lethal stroke), there were no statistically significant differences between the treatment arms. Endpoints of the quality of life category were not collected.

Taking into account the no more than minor positive effects in the morbidity categories as well as the negative effects in the side effects and considering the aforementioned methodological limitations of the REWIND study, no additional benefit is derived overall.

The randomised, actively controlled, open-label AWARD-6 study was also presented. The administration of dulaglutide compared with liraglutide, each in combination with metformin, was compared in patients whose blood glucose was not sufficiently controlled with previous metformin therapy. For the present assessment, a sub-population of patients with manifest cardiovascular disease from the AWARD-6 study was presented. Based on the AWARD-6 study, no conclusions can be drawn regarding the additional benefit of dulaglutide in this patient group because no usable data are available for the relevant sub-population.

In the overall picture, the additional benefit of dulaglutide in combination with other anti-diabetics compared with the appropriate comparator therapy is not proven for this patient group.

Patient group c)

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

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

empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents.

The randomised, double-blind, placebo-controlled REWIND study in which patients with type 2 diabetes mellitus with an HbA1c value ≤ 9.5% and manifest cardiovascular disease or high cardiovascular risk were examined was presented. The administration of dulaglutide was compared to placebo, in each case in addition to a “standard therapy” of type 2 diabetes mellitus in accordance with the national standard. The median observation period was 5 years.

In the REWIND study, liraglutide and empagliflozin, which were included in the appropriate comparator therapy, were used only to a limited extent, although both agents are explicitly recommended in the guidelines for patients with manifest cardiovascular disease or high cardiovascular risk because of their proven benefit in preventing death. Against this background, it cannot be assumed with sufficient certainty that the patients in the comparator arm received an adequate anti-diabetic treatment. The study results can therefore not be transferred to the German healthcare context with sufficient certainty. In addition, it cannot be ruled out that, for some of the patients, there may not have been a need to escalate at the start of study. Nevertheless, because of the number of patients included, the patient-relevant endpoints investigated, and the median observation period of about 5 years, the study is assessed overall for the early benefit assessment according to Section 35a SGB V.

In the morbidity category in the combined endpoint “MACE” (consisting of the individual components cardiovascular death, non-lethal myocardial infarction, and non-lethal stroke), in the individual component “non-lethal stroke”, and in the endpoint “persistent deterioration of renal function”, there is a statistically significant advantage for dulaglutide compared with the control. In contrast, dulaglutide shows a statistically significant disadvantage in the side effects category in the endpoints “discontinuation because of adverse events” and “gastrointestinal disorders”, each in the PT “nausea” and “diarrhoea”. For the remaining endpoints, including endpoints of the mortality category (overall mortality, cardiovascular death, lethal myocardial infarction, lethal stroke), there were no statistically significant differences between the treatment arms. Endpoints of the quality of life category were not collected.

Taking into account the no more than minor positive effects in the morbidity categories as well as the negative effects in the side effects and considering the aforementioned methodological limitations of the REWIND study, no additional benefit is derived overall.

In the overall picture, the additional benefit of dulaglutide in combination with other anti-diabetics compared with the appropriate comparator therapy is not proven for this patient group.

Patient group d)

Patient group d1)

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 or liraglutide) -

empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents.

For the of assessment of dulaglutide in combination therapy with insulin in the patient group of adult patients with inadequately controlled type 2 diabetes mellitus without renal failure, the results of the AWARD-4 study from the resolution of 16 July 2015 will be considered. The AWARD-4 study is a randomised, actively controlled open-label study including patients with type 2 diabetes mellitus who had an HbA1c value of ≥ 7.0% and ≤ 11.0% before entering the study with an optimised and stable insulin dosage as part of conventional insulin therapy. The combination therapy of dulaglutide with insulin lispro was compared to insulin glargine with insulin lispro for a period of 52 weeks.

In the side effects category, the combination of dulaglutide with insulin lispro shows a statistically significant advantage in the prevention of severe adverse events compared with the control arm. In contrast, there are statistically significant disadvantages for dulaglutide in combination with insulin lispro compared with control for discontinuation because of to adverse events and in the endpoint gastrointestinal disorder, especially for the PT nausea, diarrhoea, dyspepsia, loss of appetite, and vomiting. For the remaining endpoints, no statistically significant differences between the treatment arms can be identified. Quality of life data have not been submitted.

Because of the open study design, a high risk of bias is assumed for the results of all endpoints of the AWARD-4 study included.

Furthermore, the randomised, double-blind, placebo-controlled REWIND study in which patients with type 2 diabetes mellitus with an HbA1c value ≤ 9.5% and manifest cardiovascular disease or high cardiovascular risk were examined was presented. Adult patients with type 2 diabetes mellitus with a high cardiovascular risk are only a sub-group of patient group d1). Against the background of methodological limitations of the REWIND study, which do not allow the study results to be transferred to the German healthcare context with sufficient certainty and because this is only a sub-population of patient group d1), the AWARD-4 study is used to assess the additional benefit of dulaglutide in the present patient group. For the assessment of the REWIND study, reference is made to patient groups b) and c).

In the overall view, based on the AWARD-4 study, a hint for a minor additional benefit of dulaglutide in combination with insulin lispro compared with insulin glargine in combination with insulin lispro in this patient group can be derived.

Patient group d2)

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

- The optimisation of the human insulin regimen (possibly + metformin or liraglutide),

Liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of cardiovascular risk factors, in particular anti-hypertensive drugs, anticoagulants, and/or lipid-lowering agents.

The AWARD-7 study was submitted to assess the additional benefit of dulaglutide in combination with insulin lispro in the patient group of adult patients with inadequately controlled type 2 diabetes mellitus and moderate or severe renal failure.

The AWARD-7 study is a randomised, actively controlled open-label study in patients with type 2 diabetes mellitus and moderate to severe chronic kidney disease (Stage 3 and 4) in accordance with the guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NFK KDOQI) who, under conventional insulin therapy alone or in combination with oral anti-diabetics, had an HbA1c value between ≥ 7.5% and ≤ 10.5%. The administration of dulaglutide in combination with insulin lispro was compared with open therapy with insulin glargine in combination with insulin lispro. Data with a 52-week treatment duration are available for the benefit assessment.

In the side effects category, there are statistically significant advantages of dulaglutide compared with insulin glargine (in each case in combination with insulin lispro) in the prevention of non-severe, symptomatic hypoglycaemias (plasma glucose threshold ≤ 54 mg/dl as well as supplemental < 70 mg/dl) and severe hypoglycaemias. In contrast, there are statistically significant disadvantages for dulaglutide for discontinuation because of adverse events and in the endpoint gastrointestinal disorders, in particular the specific adverse events diarrhoea, nausea, and vomiting. For the remaining endpoints, including a “progression to end-stage renal disease”, no statistically significant differences between the treatment arms can be identified. Endpoints of the quality of life category were not collected.

Because of the open study design, a high risk of bias is assumed for the results of all endpoints included.

In the overall view, in this patient group, a hint for a minor additional benefit of dulaglutide in combination with insulin lispro compared with insulin glargine in combination with insulin lispro can be derived.

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

This information on the number of patients refers to 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.

The G-BA takes into account the data from the IQWiG working paper on the determination of the SHI target population for the indication type 2 diabetes mellitus in the corresponding therapeutic situations in accordance with the third validation level (https://www.iqwig.de/download/GA16-03_Routinedaten-bei-Diabetes-mellitus-Typ-2_Arbeitspapier_V1-1.pdf *[Accessed 12 December 2019]*). The figures given in the working paper refer to the data year 2013. Because of the increasing prevalence in the indication type 2 diabetes mellitus, the target population could include more patients in 2019.

The patient numbers considered include patients with validated (i.e. repeated) prescriptions of an active ingredient within the year under consideration. Hereby, all patients newly treated with anti-diabetics and those who did not receive a second prescription of an active ingredient within

the year under review are not included in the 4th quarter of the year under review. This aspect may also lead to an underestimation of the number of patients in the target population.

Because there is a lack of follow-up observations on the basis of which conclusions can be drawn about the prescription consequences of anti-diabetics in the course of the disease, a proportion of patients in patient group c) *(patients in whom diet and movement and the treatment with at least two hypoglycaemic agents (apart from insulin) do not sufficiently control the blood sugar)* is used to determine the number of patients in the next therapy stage. This corresponds to the guideline recommendations in this therapy situation that basal-supported oral therapy (BOT) may also be indicated in these patients. In principle, patients receiving monotherapy with basal insulin or monotherapy with bolus insulin are also considered.
Overall, patient group c) includes patients with a triple or multiple combination of anti-diabetics (except insulin) on one hand and patients receiving BOT, basal insulin monotherapy, and bolus insulin monotherapy on the other.

When determining the number of patients in patient group d) *(patients in whom diet and movement and the treatment (with or without another anti-diabetic agent)* do not sufficiently control the blood sugar), on the one hand, dual combinations of insulin and another anti-diabetic agent (here: metformin, sulphonylurea, another anti-diabetic agent) are considered. These dual combinations include all possible types of insulin therapy (basal, bolus, CT, ICT, other insulin combinations). On the other hand, this patient group also includes those patients who receive monotherapy with insulin as part of CT, ICT, and other insulin combinations (except monotherapy with basal insulin or bolus insulin). Because patients receiving a dual combination of basal insulin and another anti-diabetic agent as part of a BOT are also included in patient group c), a possible overestimation of patient numbers cannot be ruled out.

Regarding the percentage of patients with chronic renal insufficiency in patient group d), there are no valid data. This contributes to further uncertainty regarding the patient numbers. The resolution therefore specifies the patient groups without separate presentations of the patient numbers in the sub-populations.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Trulicity® (active ingredient: dulaglutide at the following publicly accessible link (last access: 9 June 2020):

https://www.ema.europa.eu/documents/product-information/trulicity-epar-product-information_de.pdf

The use of GLP-1 receptor agonists (e.g. dulaglutide) was associated with a risk of developing acute pancreatitis. Patients should be informed about characteristic symptoms of acute pancreatitis, and the therapy should be changed if necessary.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 June 2020).

Treatment duration and consumption:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit “days” is used to calculate the “number of

treatments/patient/year", time between individual treatments, and for the maximum treatment duration if specified in the product information.

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 anti-diabetic therapy is a continuous long-term therapy, and the titration is performed in a patient-individual manner.

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

The recommended dose of dulaglutide is 0.75 mg once a week in monotherapy and 1.5 mg once a week in adjunctive therapy.

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.

Therapy with glibenclamide should be started with 1.75–3.5 mg and increased to up to 10.5 mg glibenclamide per day if the metabolism is insufficient. The calculation is based on a potency of 3.5 mg because this dosage can cover all dosages recommended in the product information.

Therapy with glimepiride in combination with other oral anti-diabetics should be started with a low initial dose and gradually increased to the maximum tolerated daily dose depending on the targeted metabolic status. The recommended maximum dose is 6 mg; however, according to the product information, doses of glimepiride above 4 mg per day improve the effect only in isolated cases.

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 mixed insulin) is represented as "1–2 × daily" even if the application frequency can deviate in some patients. According to the product information[12] , the average insulin requirement is often 0.5–1.0 I.U. per kg body weight per day. 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

[12] Product information on Insuman® Basal, last revised: April 2019.

body weight, a mean body weight of 77.0 kg according to the official representative statistic "Microcensus 2017" is assumed[13].

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	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Patient population a), b), c), and d)				
Dulaglutide	continuously, 1 × every 7 days	52.1	1	52.1
Patient population b)				
+ metformin	continuously, 2–3 × daily	365	1	365
or				
+ glibenclamide	continuously, 1–2 × daily	365	1	365
or				
+ glimepiride	continuously, 1 × daily	365	1	365
Patient population c)				
+ metformin	continuously, 2–3 × daily	365	1	365
+ glibenclamide	continuously, 1–2 × daily	365	1	365
or				
+ glimepiride	continuously, 1 × daily	365	1	365
Patient population d)				
+ human insulin (NPH insulin)	continuously, 1–2 × daily	365	1	365

[13] German Federal Office for Statistics, Wiesbaden, 2 August 2018. Microcensus 2017: Fragen zur Gesundheit; Körpermaße der Bevölkerung 2017 [Questions about health; body measurements of the 2017 population] [online]. [Access: 1 November 2019] https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
possibly + metformin	continuously, 2–3 × daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
Glibenclamide	continuously, 1–2 × daily	365	1	365
or				
Glimepiride	continuously, 1 × daily	365	1	365
Patient population b)				
Metformin	continuously, 2–3 × daily	365	1	365
+ glibenclamide	continuously, 1–2 × daily	365	1	365
or				
+ glimepiride	continuously, 1 × daily	365	1	365
or				
+ empagliflozin	continuously, 1 × daily	365	1	365
or				
+ liraglutide	continuously, 1 × daily	365	1	365
Patient population c)				
Human insulin (NPH insulin)	continuously, 1–2 × daily	365	1	365
+ metformin	continuously, 2–3 × daily	365	1	365
or				
+ empagliflozin	continuously, 1 × daily	365	1	365
or				

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
+ liraglutide	continuously, 1 × daily	365	1	365
or				
Conventional insulin therapy				
Mixed insulin	continuously, 1–2 × daily	365	1	365
Patient population d)				
Intensified conventional insulin therapy				
Human insulin (bolus insulin) +	continuously, 3 × daily	365	1	365
Human insulin (NPH insulin)	continuously, 1–2 × daily	365	1	365
Conventional insulin therapy				
Mixed 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	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Patient populations a)					

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Dulaglutide	0.75 mg	0.75 mg	1 × 0.75 mg	52.1	52.1 × 0.75 mg
Patient populations b), c), and d)					
Dulaglutide	1.5 mg	1.5 mg	1 × 1.5 mg	52.1	52.1 × 1.5 mg
Patient populations b), c), and d)					
+ metformin hydrochloride	500 mg	1000 mg –	1 × 1,000 mg –	365	365 × 1,000 mg
	1,000 mg	3000 mg	3 × 1,000 mg		1095 × 1,000 mg
Patient populations b) and c)					
+ glibenclamide	1.75 mg	1.75 mg	1/2 × 3.5 mg	365	182.5 × 3.5 mg
	7 mg/3.5 mg	10.5 mg	3 × 3.5 mg		1095 × 3.5 mg
or					
+ glimepiride	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg
	6 mg	6 mg	1 × 6 mg		365 × 6 mg
Patient population d)					
+ 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.	365	28,105 I.U.
Appropriate comparator therapy					
Patient population a)					
Glibenclamide	1.75 mg	1.75 mg	1/2 × 3.5 mg	365	182.5 × 3.5 mg
	7 mg/3.5 mg	10.5 mg	3 × 3.5 mg		1095 × 3.5 mg
Glimepiride	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	6 mg	6 mg	1 × 6 mg		365 × 6 mg
Patient population b)					
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
+ glibenclamide	1.75 mg	1.75 mg	1/2 × 3.5 mg	365	182.5 × 3.5 mg
	7 mg/3.5 mg	10.5 mg	3 × 3.5 mg		1095 × 3.5 mg
or					
+ glimepiride	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg –
	6 mg	6 mg	1 × 6 mg		365 × 6 mg
or					
+ empagliflozin	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
	25 mg	25 mg	1 × 25 mg		365 × 25 mg
or					
+ liraglutide[14]	1.2 mg	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 c)					
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.

[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	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
+ 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
or					
+ empagliflozin	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
	25 mg	25 mg	1 × 25 mg		365 × 25 mg
or					
+ liraglutide[14]	1.2 mg	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
or					
Conventional insulin therapy					
Mixed 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.
Patient population d)					
Intensified conventional insulin therapy[15]					
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.

[15] 40–60% of the daily insulin requirement is generally covered through basal insulin; average insulin requirement: 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	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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> Mixed 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
possibly + liraglutide[14]	1.2 mg	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

<u>Costs:</u>

Costs of the medicinal product:

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

To calculate the costs of the medicinal products, the required number of packs of a particular potency was first determined on the basis of consumption. Based on the determined number of packages required, the medicinal product costs were then calculated based on the costs per package after deduction of the statutory rebates. In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130a SGB V (paragraph 1, 1a, 3a) and Section 130, paragraph 1 SGB V.

In the case of a conventional insulin therapy, the costs were based on the costs for mixed 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)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Dulaglutide 0.75 mg	12 SFI	€ 304.46	€ 1.77	€ 16.25	€ 286.44
Dulaglutide 1.5 mg	12 SFI	€ 304.46	€ 1.77	€ 16.25	€ 286.44
possibly + metformin[16] 1,000 mg	180 FCT	€ 18.84	€ 1.77	€ 0.62	€ 16.45
possibly + glibenclamide[16] 3.5 mg	180 TAB	€ 14.99	€ 1.77	€ 0.31	€ 12.91
possibly + glimepiride 1 mg[16]	180 TAB	€ 16.93	€ 1.77	€ 0.47	€ 14.69
possibly + glimepiride 6 mg[16]	180 TAB	€ 82.59	€ 1.77	€ 5.66	€ 75.16
possibly + human insulin (NPH insulin)[16]	3,000 I.U.	€ 89.70	€ 1.77	€ 6.22	€ 81.71
Appropriate comparator therapy					
Empagliflozin 10 mg	100 FCT	€ 192.40	€ 1.77	€ 10.04	€ 180.59
Empagliflozin 25 mg	100 FCT	€ 192.40	€ 1.77	€ 10.04	€ 180.59
Glibenclamide[16] 3.5 mg	180 TAB	€ 14.99	€ 1.77	€ 0.31	€ 12.91
Glimepiride 1 mg[16]	180 TAB	€ 16.93	€ 1.77	€ 0.47	€ 14.69
Glimepiride 6 mg[16]	180 TAB	€ 82.59	€ 1.77	€ 5.66	€ 75.16
Human insulin (bolus insulin)[16]	3,000 I.U.	€ 89.70	€ 1.77	€ 6.22	€ 81.71
Human insulin (NPH insulin)[16]	3,000 I.U.	€ 89.70	€ 1.77	€ 6.22	€ 81.71
Metformin[16] 1,000 mg	180 FCT	€ 18.84	€ 1.77	€ 0.62	€ 16.45
Mixed insulin[11]	3,000 I.U.	€ 89.70	€ 1.77	€ 6.22	€ 81.71
Liraglutide 18 mg	100 – 150 SD	€ 570.70	€ 1.77	€ 30.99	€ 537.94
Abbreviations: SD = single doses; FCT = film-coated tablets, I.U. = international units; SFI = solution for injection; TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 June 2020

[16] Fixed reimbursement rate

Costs for additionally required SHI services:

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

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

It is assumed that blood glucose self-monitoring is carried out 1–3 times a day when the metabolic status is stable. Because of the selective contractual agreements on blood glucose test strips, lancets, and disposable needles, the corresponding costs are charged on the basis of the cheapest pack in each case and shown on the basis of the pharmacy sales price level.

Costs for additionally required SHI services:

Designation of the therapy	Designation	Costs/package[17]	Number	Consumption/year
Medicinal product to be assessed (dulaglutide in combination with insulin (with or without oral anti-diabetic agent))				
Human insulin (NPH insulin)	Blood sugar test strips	€ 15.95	1–3 × daily	365–1,095
	Lancets	€ 4.10	1–3 × daily	365–1,095
	Disposable needles	€ 16.90	1–2 × daily	365–730
Appropriate comparator therapy				
Human insulin (NPH insulin) as well as Conventional insulin therapy (mixed insulin)	Blood sugar test strips	€ 15.95	1–3 × daily	365–1,095
	Lancets	€ 4.10	1–3 × daily	365–1,095
	Disposable needles	€ 16.90	1–2 × daily	365–730
Intensified conventional insulin therapy	Blood sugar test strips	€ 15.95	4–6 × daily	1,460–2,190
	Lancets	€ 4.10	4–6 × daily	1,460–2,190
	Disposable needles	€ 16.90	4–5 × daily	1,460–1,825
Liraglutide	Disposable needles	€ 16.90	1 × daily	365

Other services covered by SHI funds: none

[17] Number of blood glucose test strips/pack = 50 pc; number of lancets/pack = 200 pc; number of disposable needles/pack = 100 pc; representation of the cheapest pack in accordance with LAUER-TAXE®, last revised: 15 June 2020.

3. Bureaucratic costs

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 February 2019.

On 31 January 2020, the pharmaceutical company submitted a dossier for the benefit assessment of dulaglutide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, Number 6 VerfO.

By letter dated 31 January 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient dulaglutide.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 April 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 4 May 2020. The deadline for submitting written statements was 25 May 2020.

The oral hearing was held on 8 June 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 7 July 2020, and the proposed resolution was approved.

At its session on 16 July 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	12 February 2019	Determination of the appropriate comparator therapy
Working group Section 35a	3 June 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	9 June 2020	Conduct of the oral hearing
Working group Section 35a	16 June 2020 30 June 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	7 July 2020	Concluding discussion of the draft resolution

Plenum	16 July 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 16 July 2020

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

Prof. Hecken