IQWiG Reports – Commission No. A20-09

Dulaglutide (type 2 diabetes mellitus) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Dulaglutid (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 April 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
APPADL	Ability to Perform Physical Activities of Daily Living
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D VAS	visual analogue scale of the European Quality of Life-5 Dimensions
ESRD	end-stage renal disease
FPG	fasting plasma glucose
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP-1	glucagon-like peptide 1
HbA1c	haemoglobin A1c
ICT	intensified conventional treatment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IW-SP	Impact of Weight on Self-Perception
NFK KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NYHA	New York Heart Association
PG	plasma glucose
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TIA	transient ischaemic attack

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dulaglutide. The pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier on the drug to be evaluated on 2 February 2015 for the early benefit assessment. Because of new scientific findings, the G-BA now arranged for a new benefit assessment for the entire therapeutic indication of dulaglutide under inclusion of the study REWIND. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 3 February 2020.

Research question

The aim of the present report is the assessment of the added benefit of dulaglutide in comparison with the appropriate comparator therapy (ACT) for the treatment of adults with type 2 diabetes mellitus in the following approved subindications:

- Monotherapy: in patients in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is unsuitable due to intolerance or contraindications.
- Combination therapy with other drugs for the treatment of diabetes mellitus: In patients in whom diet, exercise and treatment with other blood-glucose lowering drugs do not provide adequate glycaemic control.

The G-BA distinguished between different patient groups in its specification of the ACTs. For the assessment, this resulted in 4 research questions, which are presented in Table 2.

Table 2: Research questions of the benefit assessment of dulaglutide

Research question	**Subindication**[a]	**ACT**[b]
A	Monotherapy in adults in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is unsuitable due to intolerance or contraindications	▪ Sulfonylurea (glibenclamide or glimepiride)
B	Combination therapy in adults in whom diet, exercise and treatment with one other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control	▪ Metformin + sulfonylurea (glibenclamide or glimepiride) or ▪ metformin + empagliflozin or ▪ **metformin + liraglutide**[c] or ▪ human insulin[d]
C	Combination therapy in adults in whom diet, exercise and treatment with at least 2 blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control	▪ Human insulin + metformin or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ human insulin[e]
D	Combination therapy in adults in whom diet, exercise and treatment with insulin (with or without another blood-glucose lowering drug) do not provide adequate glycaemic control	▪ Optimization of the human insulin regimen (if required + metformin or empagliflozin[c] or liraglutide[c])

a. Subdivision of the therapeutic indication according to the G-BA.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of the cardiovascular risk factors, particularly antihypertensive agents, anticoagulants and/or lipid-lowering drugs (for the operationalization, see study protocols of the relevant studies for empagliflozin and liraglutide).
d. If metformin is not tolerated or contraindicated according to the SPC.
e. If, according to the SPC, metformin, empagliflozin or liraglutide are not tolerated or contraindicated or are not sufficiently effective due to advanced type 2 diabetes mellitus.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee, SPC: Summary of Product Characteristics

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results of research question A: dulaglutide monotherapy

In its dossier, the company presented no relevant data for the assessment of dulaglutide as monotherapy in adults with type 2 diabetes mellitus in whom diet and exercise alone do not provide adequate glycaemic control, and for whom use of metformin is unsuitable due to contraindication or intolerance. This resulted in no hint of an added benefit of dulaglutide in comparison with the ACT. An added benefit is therefore not proven.

Results of research question B: dulaglutide in combination with one other blood-glucose lowering drug (except insulin)

Dulaglutide in combination with metformin in adults with manifest pre-existing cardiovascular disease

The study pool for the benefit assessment of dulaglutide in adults in whom diet, exercise and treatment with one other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control, consists of a subpopulation of the study H9X-MC-GBDE (hereinafter referred to as AWARD-6). The study compares dulaglutide with liraglutide, each in combination with metformin.

Study characteristics

The AWARD-6 study was a 2-arm, randomized, active-controlled, open-label study with a treatment duration of 26 weeks. The study included adults with type 2 diabetes mellitus in whom glycaemic control was inadequate despite an adjusted diet, exercise and pretreatment with ≥ 1500 mg/day metformin in unchanged doses for at least 3 months. Therefore, the value of the glycosylated haemoglobin A1c (HbA1c) had to range between ≥ 7.0% and ≤ 10.0% at baseline.

The AWARD-6 study investigates the comparison of dulaglutide with liraglutide. In the study, a total of 599 patients were randomly assigned to treatment with dulaglutide (N = 299) or liraglutide (N = 300), each in combination with metformin (hereinafter referred to as "dulaglutide + metformin" and "liraglutide + metformin") in a 1:1 ratio. Randomization was stratified by countries and baseline HbA1c value (≤ 8.5%; > 8.5%).

In the AWARD-6 study, treatment with dulaglutide, liraglutide and metformin was largely in line with the corresponding Summary of Product Characteristics (SPCs).

Primary outcome of the study was the change in HbA1c compared to baseline after 26 weeks of treatment. Patient-relevant secondary outcomes were "all-cause mortality" and outcomes on morbidity and adverse events (AEs).

Subpopulation relevant for the research question

In the AWARD-6 study, liraglutide + metformin was used as comparator therapy for dulaglutide. However, according to the G-BA's specification, liraglutide as ACT is an option only for patients with manifest cardiovascular disease. Therefore, the company considered a corresponding subpopulation of this study. This subpopulation comprised a total of 44 patients, 20 patients in the dulaglutide + metformin arm and 24 patients in the liraglutide + metformin arm.

Risk of bias and overall assessment of the certainty of conclusions

For the AWARD-6 study, the risk of bias across outcomes was rated as high. Based on the available data, no more than hints, e.g. of an added benefit, can be determined for the results of all included outcomes for the relevant subpopulation.

Results

Mortality

- All-cause mortality

No deaths occurred in the relevant subpopulation of the AWARD-6 study. This resulted in no hint of an added benefit of dulaglutide + metformin in comparison with liraglutide + metformin. An added benefit is therefore not proven.

Morbidity

- Health status (visual analogue scale of the European Quality of Life-5 Dimensions [EQ-5D VAS])

There were no usable data on the outcome "health status, measured using the EQ-5D VAS", for the relevant subpopulation. This resulted in no hints of an added benefit of dulaglutide + metformin in comparison with liraglutide + metformin. An added benefit is therefore not proven.

Health-related quality of life

In the AWARD-6 study, no outcome suitable to reflect the health-related quality of life was recorded. There is no hint of an added benefit of dulaglutide + metformin in comparison with liraglutide + metformin. An added benefit is therefore not proven.

Side effects

- Serious adverse events (SAEs), discontinuation due to AEs and pancreatitis acute

For the outcomes SAEs, discontinuation due to AEs and pancreatitis acute, there were no statistically significant differences between dulaglutide + metformin in comparison with liraglutide + metformin in the relevant subpopulation of the AWARD-6 study. Hence, there was no hint of greater or lesser harm from dulaglutide in comparison with liraglutide for each of these outcomes; greater or lesser harm is therefore not proven.

- Non-severe confirmed symptomatic hypoglycaemic episodes (plasma glucose [PG] ≤ 70 mg/dL and PG < 54 mg/dL) and severe hypoglycaemic episodes

For the outcomes "non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL and PG < 54 mg/dL)" and "severe hypoglycaemic episodes", there were no usable data for a comparison of dulaglutide + metformin with liraglutide + metformin for the relevant subpopulation of AWARD-6. This resulted in no hint of greater or lesser harm from dulaglutide in comparison with liraglutide; greater or lesser harm is therefore not proven.

Dulaglutide in combination with another oral antidiabetic (except metformin and insulin)

In its dossier, the company presented no relevant data on the combination of dulaglutide with another oral antidiabetic except metformin and insulin. This resulted in no hint of an added benefit of dulaglutide in comparison with the ACT. An added benefit is therefore not proven.

Dulaglutide in combination with one other blood-glucose lowering drug (except insulin) in adults without manifest pre-existing cardiovascular disease

In its dossier, the company presented no relevant data for dulaglutide in combination with one other blood-glucose lowering drug (except insulin) in adults without manifest pre-existing cardiovascular disease. This resulted in no hint of an added benefit of dulaglutide in comparison with the ACT. An added benefit is therefore not proven.

Results of research question C: dulaglutide in combination with at least 2 other blood-glucose lowering drugs (except insulin)

In its dossier, the company presented no relevant data for the assessment of dulaglutide in the combination therapy for adults with type 2 diabetes mellitus in whom diet, exercise and treatment with at least 2 blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control. This resulted in no hint of an added benefit of dulaglutide in comparison with the ACT. An added benefit is therefore not proven.

Results of research question D: dulaglutide in combination with insulin (with or without another blood-glucose lowering drug)

Dulaglutide in combination with a short-acting insulin (with or without another blood-glucose lowering drug)

The study pool for the benefit assessment of dulaglutide in adults with type 2 diabetes mellitus in whom diet, exercise and treatment with insulin (with or without another blood-glucose lowering drug) do not provide adequate glycaemic control, consists of the studies H9X-MC-GBDX (hereinafter referred to as AWARD-7) and H9X-MC-GBDD (hereinafter referred to as AWARD-4). Both studies investigated dulaglutide in combination with a short-acting insulin (insulin lispro).

The company did not present the results of the AWARD-4 study on the grounds that it had already been fully assessed by the G-BA in the first assessment of dulaglutide. Thus, the company's dossier on research question D is incomplete in terms of content.

Despite this incompleteness in terms of content, it is appropriate to assess the AWARD-7 study presented by the company in the dossier separately without meta-analysis with the study AWARD-4. In contrast to the AWARD-4 study, AWARD-7 only investigated a population with moderate or severe renal insufficiency, in which a target blood glucose level above the near-normal range was aimed at. Among other things, this resulted in a clearly lower risk of hypoglycaemic episodes compared to AWARD-4. Accordingly, conclusions on the added

benefit of dulaglutide can only be made for the subpopulation of patients from AWARD-7 with moderate or severe renal insufficiency in whom no normoglycaemia was aimed at.

Patient population with target blood glucose levels above the near-normal range (AWARD-7)

Study characteristics

AWARD-7 is a 3-arm, randomized, active-controlled, open-label phase 3 study with a treatment duration of 26 (primary treatment phase) or 52 weeks (prolonged treatment phase) which compared a combination therapy of dulaglutide and insulin lispro with a combination therapy of insulin glargine and insulin lispro.

The study included adults with type 2 diabetes mellitus and moderate or severe chronic kidney disease (stage 3 and 4) according to the guideline of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NFK KDOQI). Thereby, the stages were defined as an estimated glomerular filtration rate (eGFR) of < 60 to ≥ 15 mL/min/1.73 m².

Depending on their pretreatment (insulin with or without an oral antidiabetic), patients were switched to the study medication after randomization (day 0) based on a specified algorithm.

At the start of the study, 577 patients were randomly assigned to the study arms dulaglutide 0.75 mg/week (N = 190), dulaglutide 1.5 mg/week (N = 193) and insulin glargine (N = 194) in a 1:1:1 ratio, each in combination with insulin lispro. The study arm dulaglutide 0.75 mg/week is not relevant for the assessment and is thus not considered further. Stratification took place according to the severity of the chronic kidney disease (stage 3a, 3b or 4), macroalbuminuria (yes/no) and region.

Treatment with dulaglutide (1.5 mg/week), insulin glargine and insulin lispro was in compliance with the respective SPC. During the study, the insulin glargine dose in the control arm and the insulin lispro dose in both study arms was titrated according to a specified algorithm. The target value of < 154 mg/dL (8.6 mmol/L) or HbA1c < 7% aimed at in the AWARD-7 study corresponds to the target value recommended as an orientation aid by the NFK KDOQI Clinical Practice Guideline “Diabetes and Chronic Kidney Disease”.

Primary outcome of the study was the change in HbA1c compared to baseline after 26 weeks of treatment. Patient-relevant secondary outcomes were “all-cause mortality” and outcomes on morbidity and AEs.

Risk of bias and overall assessment of the certainty of conclusions

For the AWARD-7 study, the risk of bias across outcomes was rated as low. For the AWARD-7 study, the risk of bias for the results of all included outcomes was rated as high. Based on the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes due to the high outcome-specific risk of bias.

Results

Mortality

- All-cause mortality

Only few deaths occurred in both treatment arms. No statistically significant difference between the treatment arms was shown for the outcome "all-cause mortality". This resulted in no hint of an added benefit of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro for this outcome; an added benefit is therefore not proven.

Morbidity

- Progression to end-stage renal disease (ESRD)

No statistically significant difference between the treatment arms was shown for the outcome "progression to end-stage renal disease". This resulted in no hint of an added benefit of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro for this outcome; an added benefit is therefore not proven.

Health-related quality of life

The dossier contained no data for the outcome category "health-related quality of life". This resulted in no hint of an added benefit of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro for the outcome "health-related quality of life"; an added benefit is therefore not proven.

Side effects

- SAEs and pancreatitis acute

There was no statistically significant difference between the treatment arms for the outcomes "SAEs" and "pancreatitis acute". Hence, for these outcomes, there was no hint of greater or lesser harm from dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro; greater or lesser harm is therefore not proven.

- Discontinuation due to AEs

A statistically significant difference to the disadvantage of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro was shown for the outcome "discontinuation due to AEs". This resulted in a hint of greater harm from dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro. The events of the outcome "discontinuation due to AEs" can mainly be ascribed to gastrointestinal events.

- Gastrointestinal disorders including: diarrhoea, nausea and vomiting

There is a statistically significant difference to the disadvantage of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro each for the outcome "gastrointestinal disorders" and the events diarrhoea, nausea and vomiting included therein. This resulted in one hint of greater harm from dulaglutide + insulin lispro in comparison with insulin glargine +

insulin lispro for the outcome “gastrointestinal disorders” and the events “diarrhoea”, “nausea” and “vomiting” included therein.

- Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL and PG < 54 mg/dL) and severe hypoglycaemic episodes

A statistically significant difference in favour of dulaglutide + insulin lispro over insulin glargine + insulin lispro was shown for both operationalizations of the outcome “non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL and PG < 54 mg/dL)” and for the outcome “severe hypoglycaemic episodes”. In the course of the study, blood-glucose lowering in the intervention arm was comparable to that in the comparator arm.

However, overall, the effect in non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL) was no more than marginal. Hence, there was no hint of greater or lesser harm from dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro for this outcome; greater or lesser harm is therefore not proven.

Overall, a hint of lesser harm from dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro each resulted for non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL) and for the outcome “severe hypoglycaemic episodes”.

Patient population with the treatment goal of near-normal blood-glucose levels (AWARD-4 study)

The content of the company’s dossier was incomplete regarding the combination of dulaglutide with another short-acting insulin (with or without another blood-glucose lowering drug) and the treatment goal of near-normal blood-glucose levels.

Overall, this resulted in no proof of an added benefit of dulaglutide + a short-acting insulin (with or without another blood-glucose lowering drug) and the treatment goal of near-normal blood-glucose levels versus the ACT “optimization of the human insulin regimen”.

Dulaglutide in combination with a long-acting insulin (with or without another blood-glucose lowering drug)

The company presented no data on the combination of dulaglutide with a long-acting insulin (with or without another blood-glucose lowering drug).

Overall, this resulted in no proof of an added benefit of dulaglutide + a long-acting insulin (with or without another blood-glucose lowering drug) versus the ACT “optimization of the human insulin”.

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

Based on the results presented, probability and extent of the added benefit of the drug dulaglutide in comparison with the ACT are assessed as follows:

Research question A: dulaglutide monotherapy

An added benefit of dulaglutide is not proven for this research question, since relevant data for the assessment of the added benefit of dulaglutide monotherapy versus the ACT are not available for adults with type 2 diabetes mellitus in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is unsuitable due to intolerance or contraindications.

Research question B: dulaglutide in combination with one other blood-glucose lowering drug (except insulin)

Dulaglutide in combination with metformin in adults with manifest pre-existing cardiovascular disease

Overall, the assessment revealed neither positive nor negative effects of dulaglutide in comparison with liraglutide.

In summary, an added benefit of dulaglutide + metformin over liraglutide + metformin has not been proven for patients with type 2 diabetes mellitus with manifest pre-existing cardiovascular disease, in whom diet, exercise and treatment with one other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control.

Dulaglutide in combination with metformin in adults without manifest pre-existing cardiovascular disease

Due to lack of relevant data, an added benefit of dulaglutide versus the ACT has not been proven for dulaglutide in combination with metformin in adults without manifest cardiovascular disease.

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

Dulaglutide in combination with one other blood-glucose lowering antidiabetic (except metformin and insulin)

Due to lack of relevant data, an added benefit of dulaglutide versus the ACT has not been proven for dulaglutide in combination with one other blood-glucose lowering drug (except metformin and insulin).

Research question C: dulaglutide in combination with at least 2 other blood-glucose lowering drugs (except insulin)

Since no relevant data are available for the assessment of the added benefit of dulaglutide in comparison with the ACT in adults with type 2 diabetes mellitus in whom diet, exercise and treatment with at least two other blood glucose-lowering drugs (except insulin) do not provide adequate glycaemic control, an added benefit of dulaglutide has not been proven for this research question.

Research question D: dulaglutide in combination with insulin (with or without another blood-glucose lowering drug)

Dulaglutide in combination with a short-acting insulin (with or without another blood-glucose lowering drug)

Patient population with target blood glucose levels above the near-normal range (AWARD-7 study)

The overall consideration showed both positive and negative effects of dulaglutide + insulin lispro versus insulin glargine + insulin lispro, each with the same certainty of results ("hint"). However, in summary, the positive effects, which are particularly shown by the hint of lesser harm in the outcome "severe hypoglycaemic episodes" with the extent "major" (outcome category "serious/severe side effects"), outweighed the negative ones.

Overall, this resulted in a hint of considerable added benefit of dulaglutide over insulin glargine, each in combination with insulin lispro, for patients with type 2 diabetes mellitus in whom diet, exercise and treatment with insulin (with or without another blood-glucose lowering drug) do not provide adequate glycaemic control. However, the added benefit only applies to patients for whom treatment with a short-acting insulin and target blood glucose levels above the near-normal range are aimed at.

Patient population with the treatment goal of near-normal blood-glucose levels (AWARD-4 study)

The content of the company's dossier was incomplete regarding the combination of dulaglutide with a short-acting insulin (with or without another blood-glucose lowering drug) and the treatment goal of near-normal blood-glucose levels.

Overall, this resulted in no proof of an added benefit of dulaglutide + a short-acting insulin (with or without another blood-glucose lowering drug) and the treatment goal of near-normal blood-glucose levels versus the ACT "optimization of the human insulin regimen".

Dulaglutide in combination with a long-acting insulin (with or without another blood-glucose lowering drug)

The company presented no data on the combination of dulaglutide with a long-acting insulin (with or without another blood-glucose lowering drug).

Overall, this resulted in no proof of an added benefit of dulaglutide + a long-acting insulin (with or without another blood-glucose lowering drug) versus the ACT "optimization of the human insulin regimen".

Summary

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

Table 3: Dulaglutide – probability and extent of the added benefit in adults with type 2 diabetes mellitus

Research question	**Subindication**[a]	**ACT**[b]	**Probability and extent of added benefit**
A	Monotherapy in adults in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is unsuitable due to intolerance or contraindications	▪ Sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Combination therapy in adults in whom diet, exercise and treatment with one other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control	▪ Metformin + sulfonylurea (glibenclamide or glimepiride) or ▪ metformin + empagliflozin or ▪ **metformin + liraglutide**[c] or ▪ human insulin[d]	Added benefit not proven
C	Combination therapy in adults in whom diet, exercise and treatment with at least 2 blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control	▪ Human insulin + metformin or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ human insulin[e]	Added benefit not proven
D	Combination therapy in adults in whom diet, exercise and treatment with a short-acting insulin (with or without other blood-glucose lowering drugs) do not provide adequate glycaemic control	▪ Optimization of the human insulin regimen (if required + metformin or empagliflozin[c] or liraglutide[c])	*Treatment goal near-normal blood glucose levels:* added benefit not proven
			Treatment goal non near-normal blood glucose levels[f]: hint of a considerable added benefit
	Combination therapy in adults in whom diet, exercise and treatment with a long-acting insulin (with or without another blood-glucose lowering drug) do not provide adequate glyceamic control		Added benefit not proven

a. Subdivision of the subindication according to the G-BA.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of the cardiovascular risk factors, particularly antihypertensive agents, anticoagulants and/or lipid-lowering drugs (for the operationalization, see study protocols of the relevant studies for empagliflozin and liraglutide).
d. If metformin is not tolerated or contraindicated according to the SPC.
e. If, according to the SPC, metformin and empagliflozin[c] or liraglutide[c] are not tolerated or contraindicated or are not sufficiently effective due to advanced type 2 diabetes mellitus.
f. Therapy targeted at a uniform mean fasting plasma glucose (FPG) level < 154 mg/dL (100 to 150 mg/dL for insulin glargine or 120 to 180 mg/dL for insulin lispro).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Research question additionally investigated by the company (study REWIND)

In its dossier, the company investigated an additional research question: determination of the extent of added benefit of dulaglutide in monotherapy or in combination therapy with another blood-glucose lowering drug and a standard therapy in adult patients with type 2 diabetes mellitus with increased cardiovascular risk in comparison with a standard therapy. The company defined a standard therapy as individual, antidiabetic and cardiovascular concomitant treatment in accordance with national or international standard. The company presented the REWIND study for this research question.

The study REWIND is a randomized, double-blind, placebo-controlled parallel-group study that included adult patients with type 2 diabetes mellitus with an HbA1c value of ≤ 9.5% and an increased cardiovascular risk. The study compared treatment with dulaglutide in addition to ongoing antidiabetic therapy versus standard antidiabetic therapy.

Adult patients with type 2 diabetes mellitus and increased cardiovascular risk are comprised in the therapeutic indication of dulaglutide and thus as subgroups in all 4 research questions mentioned above. In accordance with the G-BA's specification, the added benefit for these subpopulations also has to be shown in comparison with the respective ACT. The company did not present such analyses. However, due to the way it was conducted, the REWIND study is unsuitable for this purpose, too. Irrespective of this, the REWIND study is also unsuitable for the comparison with standard therapy intended by the company:

- On the one hand, it is questionable whether a majority of the patients required escalation of their antidiabetic therapy at all, because the blood glucose level had potentially not been inadequate at baseline (proportion of patients with HbA1c values below 7.5%: approx. 56%); since dulaglutide is only approved for patients with inadequate blood glucose level, the REWIND study would thus have been conducted largely outside the approval of dulaglutide. On the other hand, equivalent glycaemic control was not achieved in the treatment arms in patients in whom the need for escalation was probable due to inadequate blood glucose control (HbA1c value ≥ 7.5%, estimated proportion 44%); therefore, the relevant study objective was not achieved.
- Moreover, differences between the treatment groups in favour of dulaglutide were also shown for the mean change in systolic blood pressure compared to baseline over the entire course of the study, although comparable blood pressure control between the treatment groups would have been expected based on the study requirements. Since the blood pressure has great influence on the cerebrovascular and cardiovascular outcomes as well as on the kidney outcomes, the results can be distorted in favour of dulaglutide.

Nevertheless, statistically significant results in favour of dulaglutide + standard therapy in comparison with placebo + standard therapy were shown for the following outcomes:

- Nonfatal stroke
- persistent deterioration of renal function

There are statistically significant results to the disadvantage of dulaglutide + standard therapy in comparison with placebo + standard therapy for the following outcomes:

- Discontinuation due to AEs
- gastrointestinal disorders (System Organ Class [SOC], AE)
  - Nausea (Preferred Term [PT], AE)
  - Vomiting (PT, AE)

No statistically significant differences between the treatment groups were shown for the other outcomes presented.

2.2 Research question

The aim of the present report is the assessment of the added benefit of dulaglutide in comparison with the ACT for the treatment of adults with type 2 diabetes mellitus in the following approved subindications:

- Monotherapy: in patients in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is unsuitable due to intolerance or contraindications.
- Combination therapy with other drugs for the treatment of diabetes mellitus: In patients in whom diet, exercise and treatment with other blood-glucose lowering drugs do not provide adequate glycaemic control.

In its specification of the ACT, the G-BA distinguished between different patient groups. This resulted in 4 research questions, which are presented in Table 4.

Table 4: Research questions of the benefit assessment of dulaglutide

Research question	**Subindication**[a]	**ACT**[b]
A	Monotherapy in adults in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is unsuitable due to intolerance or contraindications	▪ Sulfonylurea (glibenclamide or glimepiride)
B	Combination therapy in adults in whom diet, exercise and treatment with one other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control	▪ Metformin + sulfonylurea (glibenclamide or glimepiride) or ▪ metformin + empagliflozin or ▪ **metformin + liraglutide**[c] or ▪ human insulin[d]
C	Combination therapy in adults in whom diet, exercise and treatment with at least 2 blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control	▪ Human insulin + metformin or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ human insulin[e]
D	Combination therapy in adults in whom diet, exercise and treatment with Insulin (with or without another blood-glucose lowering drug) do not provide adequate glycaemic control	▪ Optimization of the human insulin regimen (if required + metformin or empagliflozin[c] or liraglutide[c])

a. Subdivision of the therapeutic indication according to the G-BA.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of the cardiovascular risk factors, particularly antihypertensive agents, anticoagulants and/or lipid-lowering drugs (for operationalization, see study protocols of the relevant studies on empagliflozin [3] and liraglutide [4]).
d. If metformin is not tolerated or contraindicated according to the SPC.
e. If, according to the SPC, metformin, empagliflozin or liraglutide are not tolerated or contraindicated or are not sufficiently effective due to advanced type 2 diabetes mellitus.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The company followed the respective ACT specified by the G-BA for the research question presented in Table 4.

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

Research question additionally investigated by the company

In its dossier, the company investigated an additional research question: determination of the extent of added benefit of dulaglutide in monotherapy or in combination therapy with another blood-glucose lowering drug and a standard therapy in adult patients with type 2 diabetes mellitus with increased cardiovascular risk in comparison with a standard therapy. The

company defined standard therapy as individual, antidiabetic and cardiovascular concomitant treatment in accordance with national or international standard. For this research question, the company presented the study REWIND [5-13].

Adult patients with type 2 diabetes mellitus and increased cardiovascular risk are comprised in the therapeutic indication of dulaglutide and thus as subgroups in all 4 research questions mentioned above. In accordance with the G-BA's specification, the added benefit for these subpopulations also has to be shown in comparison with the respective ACT. The company did not present such analyses. However, due to the way it was conducted, the REWIND study is unsuitable for this purpose, too. Irrespective of this, the REWIND study is also unsuitable for the comparison with standard therapy intended by the company (see Appendix A of the full dossier assessment).

Due to the size and the outcomes investigated (particularly cardiovascular events and all-cause mortality), the study REWIND is described in Appendix A of the full dossier assessment.

2.3 Research question A: dulaglutide monotherapy

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dulaglutide (status: 18 November 2019)
- bibliographical literature search on dulaglutide (last search on 4 November 2019)
- search in trial registries for studies on dulaglutide (last search on 5 November 2019)

To check the completeness of the study pool:

- search in trial registries for studies on dulaglutide (last search on 14 February 2020)

The check of the completeness of the study pool produced no RCTs on the direct comparison of dulaglutide with the ACT for research question A (dulaglutide monotherapy). This assessment concurs with that of the company.

However, the company stated that results relevant for the patient population considered in the present therapeutic indication can be found in the REWIND study presented in Module 4 E of the dossier. This assessment was inadequate. The REWIND study was irrelevant for the assessment of the added benefit of dulaglutide in the present research question. This is particularly due to the fact that REWIND permits no comparison with the ACT specified by the G-BA. Moreover, for the few patients in the REWIND study who had not been treated with medication before the start of the study, it was not shown that the use of metformin was not suitable due to intolerance or contraindications (see information on the REWIND study in Appendix A of the full dossier assessment).

2.3.2 Results on added benefit

In its dossier, the company presented no relevant data for the assessment of dulaglutide as monotherapy in adults with type 2 diabetes mellitus in whom diet and exercise alone do not provide adequate glycaemic control, and for whom use of metformin is unsuitable due to intolerance or contraindications. This resulted in no hint of an added benefit of dulaglutide in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

An added benefit of dulaglutide is not proven for this research question, since relevant data for the assessment of the added benefit of dulaglutide monotherapy versus the ACT are not available for adults with type 2 diabetes mellitus in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is unsuitable due to intolerance or contraindications.

This deviates from the company's assessment. In research question A, the company derived considerable added benefit of dulaglutide versus the ACT for patients with an increased cardiovascular risk on the basis of the REWIND study presented by it in Module 4 E of the dossier.

2.4 Research question B: dulaglutide in combination with one other blood-glucose lowering drug (except insulin)

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dulaglutide (status: 18 November 2019)
- bibliographical literature search on dulaglutide (last search on 4 November 2019)
- search in trial registries for studies on dulaglutide (last search on 5 November 2019)

To check the completeness of the study pool:

- search in trial registries for studies on dulaglutide (last search on 14 February 2020)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: dulaglutide + metformin vs liraglutide + metformin

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
H9X-MC-GBDE (AWARD-6[c])	Yes	Yes	No	Yes [14]	Yes [15-18]	Yes [19]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of dulaglutide in adults in whom diet, exercise and treatment with another blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control, consists of the study H9X-MC-GBDE (hereinafter referred to as AWARD-6). The study compares dulaglutide with liraglutide, each in combination with metformin. The study pool concurs with that of the company.

Since liraglutide (+ metformin) only constitutes an ACT for patients with manifest cardiovascular disease, the AWARD-6 study only permits conclusions on the added benefit of dulaglutide for this subpopulation of research question B. Accordingly, the company presented an analysis of this subpopulation of patients with manifest pre-existing cardiovascular disease from the AWARD-6 study (see also Section 2.4.1.2).

Within research question B, the company presented no relevant studies for the combination of dulaglutide and metformin in adults without manifest pre-existing cardiovascular disease as well as for dulaglutide in combination with another blood-glucose lowering drug (except metformin and insulin).

2.4.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: dulaglutide + metformin vs. liraglutide + metformin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AWARD-6	RCT, open-label, parallel	Adults with inadequately controlled type 2 diabetes mellitus despite adapted diet and exercise ▪ pretreated with metformin (≥ 1500 mg/day, stable dosage during the last 3 months) ▪ HbA1c value at baseline: ≥ 7.0% and ≤ 10.0% ▪ without renal insufficiency[b]	Dulaglutide + metformin (N = 299) liraglutide + metformin (N = 300) relevant subpopulation thereof: dulaglutide + metformin (n = 20) liraglutide + metformin (n = 24)	Screening: 2 weeks treatment: 26 weeks follow-up observation: 4 weeks	62 centres in Czech Republic, Germany, Hungary, Mexico, Poland, Puerto Rico, Romania, Slovak Republic, Spain, USA 07/2012–11/2013	Primary: change in HbA1c compared to baseline after 26 weeks of treatment secondary: mortality, morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Exclusion at serum creatinine levels ≥ 1.5 mg/dL (men) or ≥ 1.4 mg/dL (women) or creatinine clearance of < 60 mL/min at baseline.

AE: adverse event; HbA1c: glycosylated haemoglobin A1c; n: number of randomized patients in the relevant subpopulation; N: Number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: dulaglutide + metformin vs. liraglutide + metformin

Study	Intervention	Comparison
AWARD-6	Dulaglutide 1.5 mg SC, once weekly + metformin ≥ 1500 mg[a, b] orally, daily	Liraglutide 1.8 mg SC, once daily + metformin ≥ 1500 mg[a, b] orally, daily
		Liraglutide titration scheme: ▪ initiation (week 1): 0.6 mg/day liraglutide SC ▪ increase (week 2): 1.2 mg/day liraglutide SC ▪ final (week 3–26[c]): 1.8 mg/day liraglutide SC
	Pretreatment: ▪ metformin at a stable dosage of ≥ 1500 mg/day for at least 3 months before start of study **non-permitted concomitant treatment:** ▪ other GLP-1 receptor agonist or DPP-4 inhibitors ▪ systemic glucocorticoids > 14 days[d] ▪ drugs to promote weight loss **subsequent treatment during follow-up:** ▪ antihyperglycaemic treatment regimen at the physician's discretion. Treatment with other GLP-1 receptor agonists and DPP-4 inhibitors was excluded	

a. At most up to the respective locally approved dose; the highest dose administered within AWARD-6 was 3000 mg/day.
b. Permitted dose adjustments after randomization: discontinuation or dose reduction in case of increased risk of hypoglycaemia or in case of a contraindication mentioned in the country-specific SPC, e.g. renal insufficiency; dose increase in case of severe persistent hyperglycaemia.
c. End of the treatment phase.
d. Topical, intraocular or intranasal application was permitted.

DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide 1; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus

Study characteristics

The AWARD-6 study was a 2-arm, randomized, active-controlled, open-label study with a treatment duration of 26 weeks. The study included adults with type 2 diabetes mellitus in whom glycaemic control was inadequate despite an adjusted diet, exercise and pretreatment with ≥ 1500 mg/day metformin in unchanged doses for at least 3 months. Therefore, the value of the HbA1c value had to range between ≥ 7.0% and ≤ 10.0% at baseline.

The AWARD-6 study investigates the comparison of dulaglutide with liraglutide. In the study, a total of 599 patients were randomly assigned to treatment with dulaglutide (N = 299) or liraglutide (N = 300), each in combination with metformin (hereinafter referred to as dulaglutide + metformin and liraglutide + metformin) in a 1:1 ratio. Randomization was stratified by countries and baseline HbA1c value (≤ 8.5%; > 8.5%).

Primary outcome of the study was the change in HbA1c compared to baseline after 26 weeks of treatment. Patient-relevant secondary outcomes were "all-cause mortality" and outcomes on morbidity and AEs.

Treatment with the study medication

In the AWARD-6 study, treatment with dulaglutide was in compliance with the approval [20].

In the control arm, the daily liraglutide dose was increased from 0.6 mg to 1.2 mg and then to the approved maximum dose of 1.8 mg at one-week intervals for all patients. The mandatory dose increase to 1.8 mg for all patients represents a forced titration regimen in comparison to the data in the SPC. According to the SPC [21], an increase of the daily liraglutide dose from 1.2 mg to 1.8 mg was only intended as an option for some patients. The decision on this was to be based on the treatment success. However, according to the study documents, a check of the treatment success in the liraglutide titration phase of the AWARD-6 study was not intended.

For the patients in the AWARD-6 study, the continuation of their respective metformin therapy at a dosage of ≥ 1500 mg/day up to the locally approved maximum dosage in addition to the study medication was planned in both study arms. The maximum dosage of metformin administered in the AWARD-6 study was 3000 mg/day, which is the highest dosage approved in Germany [22].

Following treatment with the study medication, the antihyperglycaemic treatment regimen for the follow-up phase could be selected by the treating physician. Treatment with other glucagon-like-peptide-1 (GLP-1) receptor agonists and with dipeptidylpeptidase-4 (DPP-4) inhibitors was excluded.

Subpopulation relevant for the research question

In the AWARD-6 study, liraglutide + metformin was used as comparator therapy for dulaglutide. However, according to the G-BA's specification, liraglutide as ACT is an option only for patients with manifest cardiovascular disease. For the operationalization of a manifest cardiovascular disease, the G-BA refers to the study protocol of the LEADER study [4].

Manifest pre-existing cardiovascular disease

The AWARD-6 study included not only patients with manifest cardiovascular disease, but also patients without such disease. The company therefore considered a subpopulation from this study.

In contrast to the G-BA's specification, the company did not follow the study protocol when forming the subpopulation of the LEADER study, but on the inclusion criteria of the long-term study REWIND that investigated patients with increased cardiovascular risk (see Appendix A of the full dossier assessment). The company did not justify this deviating approach.

Based on the REWIND study, the company included those patients of the AWARD-6 study in the subpopulation in whom, according to the information in the case report form, at least one of the following events had occurred before the study started:

- myocardial infarction

- stroke
- coronary revascularization
- carotid revascularization
- arterial revascularization of the lower limbs
- hospitalization due to unstable angina pectoris

This subpopulation of the company comprised a total of 44 patients, i.e. 20 patients in the dulaglutide + metformin arm and 24 patients in the liraglutide + metformin arm.

In addition to the criteria used by the company, the LEADER study lists further criteria for the definition of a manifest cardiovascular disease:

- Previous transient ischaemic attack (TIA)
- > 50% stenosis of the coronary artery, carotid artery or an artery of the lower limbs
- History of symptomatic coronary heart disease or unstable angina pectoris with changes in the electrocardiogram (ECG)
- Asymptomatic cardiac ischemia
- Chronic cardiac insufficiency (New York Heart Association [NYHA] class II–III)
- Chronic renal insufficiency

For the present benefit assessment, it was investigated whether the AWARD-6 study includes patients who meet the criteria additionally mentioned in the LEADER study and should thus also be included in the relevant subpopulation.

The review showed that in addition to the 44 patients considered by the company in the subpopulation, another 15 patients in the study had documented pre-existing cardiovascular disease. Although 13 of these 15 patients had documented peripheral arterial occlusive disease and/or coronary heart disease (as the only pre-existing cardiovascular disease), the definition of a manifest disease (at least 50% stenosis) was not necessarily given. Therefore, it cannot be assumed with certainty that these patients had a manifest pre-existing cardiovascular disease.

Moreover, the company excluded one study participant of each treatment arm of the total population of the AWARD-6 study, for which only a TIA (and no other previous cardiovascular disease) was documented, from its subpopulation. However, within the subpopulation, these two patients only account for about 5% or 4% of the respective study arm.

Overall, the company’s approach therefore has no consequences for the present benefit assessment.

Concomitant drug treatment of the cardiovascular risk factors

The further requirement for the use of liraglutide as ACT is that patients with manifest pre-existing cardiovascular disease must receive drug treatment for their cardiovascular risk factors.

Table 10 presents the concomitant cardiovascular treatments for the subpopulation of the AWARD-6 study relevant for research question B. The data suggest that comprehensive drug use including antihypertensives, lipid-lowering or blood-thinning agents for the treatment of cardiovascular risk factors was ensured.

Summary

Overall, the company's approach to form a subpopulation from the AWARD-6 study is appropriate for the present research question B.

Patient characteristics

Table 8, Table 9 and Table 10 show the characteristics of the patients in the relevant subpopulation in the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: dulaglutide + metformin vs. liraglutide + metformin

Study **Characteristics** **Category**	**Dulaglutide + metformin** **N[a] = 20**	**Liraglutide + metformin** **N[a] = 24**
AWARD-6 (subpopulation)		
Age [years], mean (SD)	62 (6)	60 (8)
Sex [F/M], %	20/80	13/88
Family origin, n (%)		
Native American or Alaskan	0 (0)	0 (0)
Asian	0 (0)	0 (0)
Black or African American	1 (5.0)	1 (4.2)
Native Hawaiians or other Pacific Islanders	0 (0)	0 (0)
White	19 (95.0)	23 (95.8)
Several	0 (0)	0 (0)
Body weight [kg], mean (SD)	98.1 (13.9)	95.9 (16.6)
BMI [kg/m²], mean (SD)	33.5 (3.7)	32.9 (4.5)
Diabetes duration (years) at baseline, mean (SD)	9.1 (7.6)	6.9 (6.3)
HbA1c (%) at baseline, n (%)		
HbA1c ≤ 8.5	16 (80.0)	20 (83.3)
HbA1c > 8.5	4 (20.0)	4 (16.7)
HbA1c (%) at baseline, mean (SD)	7.9 (0.8)	7.9 (0.6)
Treatment discontinuation, n (%)	1 (5.0)	2 (8.3)
Study discontinuation, n (%)	0 (0)	1 (4.2)

a. Number of randomized patients in the subpopulation relevant for research question B.

BMI: body mass index; F: female; HbA1c: glycosylated haemoglobin A1c; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 9: Information on pre-existing cardiovascular disease before study inclusion – RCT, direct comparison: dulaglutide + metformin vs. liraglutide + metformin

Study Characteristics Category	**Patients with pre-existing cardiovascular disease before study inclusion[a] n (%)**	
	dulaglutide + metformin N[b] = 20	**liraglutide + metformin N[b] = 24**
AWARD-6 (subpopulation)		
Hospitalization due to unstable angina pectoris	4 (20.0)	2 (8.3)
Hospitalization due to cardiac failure	2 (10.0)	1 (4.2)
Coronary heart disease[c]	12 (60.0)	8 (33.3)
Myocardial infarction	9 (45.0)	12 (50.0)
Peripheral arterial occlusive disease[d]	3 (15.0)	4 (16.7)
Revascularization		
Arterial revascularization of the lower limbs	0 (0)	2 (8.3)
Carotid revascularization	0 (0)	2 (8.3)
Coronary revascularization	11 (55.0)	10 (41.7)
Stroke	3 (15.0)	7 (29.2)
TIA	1 (5.0)	3 (12.5)

a. Several pre-existing cardiovascular diseases could be documented per patient.
b. Number of randomized patients in the subpopulation relevant for the research question B. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Documented in patients with further pre-existing cardiovascular disease (except peripheral arterial occlusive disease).
d. Documented in patients with further pre-existing cardiovascular disease (except coronary heart disease).

n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; TIA: transient ischaemic attack; vs.: versus

Table 10: Information regarding concomitant medication – RCT, direct comparison: dulaglutide + metformin vs. liraglutide + metformin

Study Characteristics Category	Patients with concomitant medication n (%)	
	dulaglutide + metformin N[a] = 20	liraglutide + metformin N[a] = 24
AWARD-6 (subpopulation)		
Antihypertensive medications	19 (95.0)	21 (87.5)
ACE inhibitors or angiotensin receptor blockers	12 (60.0)	18 (75.0)
ACE inhibitors	10 (50.0)	14 (58.3)
Angiotensin receptor blocker	2 (10.0)	5 (20.8)
Antiadrenergic agents	1 (5.0)	4 (16.7)
Beta-blockers	15 (75.0)	15 (62.5)
Calcium channel blockers	5 (25.0)	6 (25.0)
Diuretics	13 (65.0)	11 (45.8)
Renin inhibitors	0 (0)	0 (0)
Other	0 (0)	0 (0)
Lipid-lowering drugs	16 (80.0)	19 (79.2)
HMG-CoA reductase inhibitors	16 (80.0)	17 (70.8)
Niacin	0 (0)	1 (4.2)
Fibrates	1 (5.0)	4 (16.7)
Bile acid sequestrants	1 (5.0)	0 (0)
Cholesterol uptake inhibitors	1 (5.0)	0 (0)
Blood-thinning drugs	16 (80.0)	21 (87.5)
Aspirin	14 (70.0)	16 (66.7)
Platelet aggregation inhibitors	3 (15.0)	10 (41.7)
Vitamin K antagonist	1 (5.0)	2 (8.3)
Antithrombotics	0 (0)	0 (0)
Other	0 (0)	0 (0)
Anti-inflammatory drugs	5 (25.0)	2 (8.3)
Nonsteroidal anti-inflammatory drug (NSAID)	5 (25.0)	2 (8.3)
COX-2 inhibitors	0 (0)	0 (0)
Other	0 (0)	0 (0)
Cardiac medication	6 (30.0)	3 (12.5)
Inotropic substances	0 (0)	0 (0)
Antiarrhythmics	1 (5.0)	0 (0)
Stimulants	1 (5.0)	1 (4.2)
Vasodilators (nitrates and others)	0 (0)	2 (8.3)
Other	5 (25.0)	1 (4.2)

a. Number of randomized patients in the subpopulation relevant for the research question B. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

ACE: angiotensin converting enzyme; COX-2: cyclooxygenase-2; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme-A; n: number of patients in the category; N: number of randomized patients; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; vs.: versus

Distribution of the characteristics of the patients in the relevant subpopulation was sufficiently similar between the treatment arms.

Most patients of the subpopulation with manifest pre-existing cardiovascular disease relevant for research question B in the AWARD-6 study were male and white. The mean age of the patients was about 60 years; at baseline, they had a body weight of about 98 kg or 96 kg and a mean HbA1c value of 7.9% after an average diabetes duration of about 9 years in the dulaglutide + metformin arm and about 7 years in the liraglutide + metformin arm.

The majority of the patients in the relevant subpopulation received antihypertensive agents (95.0% or 87.5%), lipid-lowering drugs (80.0% or 79.2%) or blood-thinning drugs (80.0% or 87.5%) as concomitant medication.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: dulaglutide + metformin vs. liraglutide + metformin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
AWARD-6	Yes	Yes	No	No	Yes	No[a]	High

a. Questionable structural equality of the treatment groups in the analysed subpopulation.

RCT: randomized controlled trial; vs.: versus

Due to the questionable structural equality of the treatment groups in the analysed sub-population, the risk of bias across outcomes for the AWARD-6 study was rated as high (see Section 2.8.3.4.2 of the full dossier assessment). This subpopulation was formed based on post hoc criteria and resulted in a relatively small sample size, in which particularly the patient profiles regarding their pre-existing cardiovascular diseases differed between the treatment arms (see Table 9). This deviates from the company's assessment, which assessed the risk of bias across outcomes as low.

Limitations additionally resulting from the open-label study design are described under outcome-specific risk of bias in Section 2.4.2.2.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.3.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - health status (EQ-5D VAS)
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - non-severe confirmed symptomatic hypoglycaemic episodes
    - PG < 54 mg/dL
    - PG ≤ 70 mg/dL
  - severe hypoglycaemic episodes
  - pancreatitis acute (adjudicated events)
  - possibly, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 B) (see Section 2.8.3.4.3.2 of the full dossier assessment). The outcomes “change in HbA1c”, “change in body weight” and “change in body mass index (BMI)” were to be presented as supplementary information for the present benefit assessment. However, data on the change in body weight and BMI were not available for the relevant subpopulation; the available data on the change in HbA1c were not usable.

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: dulaglutide + metformin vs. liraglutide + metformin

Study	Outcomes								
	All-cause mortality	**Health status (EQ-5D VAS)**	**Health-related quality of life**	**SAEs**	**Discontinuation due to AEs**	**Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)**	**Non-severe confirmed symptomatic hypoglycaemic episodes in total (PG ≤ 70 mg/dL)**	**Severe hypoglycaemic episodes**	**Pancreatitis acute[c]**
AWARD-6	Yes	No[a]	No[b]	Yes	Yes	No[a]	No[a]	No[a]	Yes

a. Usable data are not available since the analysis only considered data up to the use of rescue medication. Analyses under consideration of all relevant data are only available for the total population (see Section 2.8.3.4.3.2 of the full dossier assessment).
b. No data available (see Section 2.8.3.4.3.2 of the full dossier assessment).
c. Adjudicated results based on 2 of 3 of the following criteria: 1: abdominal pain typical for pancreatitis acute, 2: three-fold increase in serum amylase and/or serum lipase, and 3: CT or MRI findings.

AE: adverse event; CT: computed tomography; EQ-5D: European Quality of Life-5 Dimensions; MRI: magnetic resonance imaging; PG: plasma glucose; RCT: randomized controlled; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: dulaglutide + metformin vs. liraglutide + metformin

Study	Study level	Outcomes								
		All-cause mortality	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)	Non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 54 mg/dL)	Severe hypoglycaemic episodes	Pancreatitis acute[e]
AWARD-6	H	H[a]	-[b]	-[c]	H[a]	H[a, d]	-[b]	-[b]	-[b]	H[a]

a. High risk of bias at study level.
b. No usable data available.
c. No data available
d. Lack of blinding in subjective recording of outcomes.
e. Adjudicated results based on 2 of 3 of the following criteria: 1: abdominal pain typical for pancreatitis acute, 2: Three-fold increase in serum amylase and/or serum lipase, and 3: CT or MRI findings.

AE: adverse event; CT: computed tomography; EQ-5D: European Quality of Life-5 Dimensions; H: high; MRI: magnetic resonance imaging; PG: plasma glucose; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

For AWARD-6, there is a high risk of bias at study level. Therefore, the risk of bias for the results on the outcomes "all-cause mortality", "SAEs" and "pancreatitis acute" was rated as high. Another reason for the high risk of bias for results on the outcome "discontinuation due to AEs" is the lack of blinding in subjective recording of outcomes.

The outcome-specific risk of bias for the outcomes "health status (EQ-5D VAS)", "health-related quality of life", "non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL and < 54 mg/dL)" and "severe hypoglycaemic episodes" was not assessed. Usable data for the outcomes "health status (EQ-5D VAS)", "non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL and PG < 54 mg/dL)" as well as "severe hypoglycaemic episodes" are not available for the subpopulation relevant for research question B, because the analyses presented by the company contained no data of patients after the administration of the rescue medication. Outcomes suitable to reflect the health-related quality of life were not recorded in the AWARD-6 study (see Section 2.8.3.4.3.2 of the full dossier assessment).

The assessment deviates from that of the company, which rated the risk of bias for the results on all mentioned outcomes except for "discontinuation due to AEs" and "health status (EQ-5D VAS)" as low. The company rated the risk of bias for results on the outcomes "discontinuation

due to AEs" and "health status (EQ-5D VAS)" as high, because these outcomes were recorded in an unblinded manner.

2.4.2.3 Results

Table 14 and Table 15 summarize the results on REWIND-6 study. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Tables with the common AEs, SAEs and discontinuations due to AEs can be found in Appendix B.1 of the full dossier assessment.

Table 14: Results (mortality, side effects) – RCT, direct comparison: dulaglutide + metformin vs. liraglutide + metformin

Study Outcome category	Dulaglutide + metformin		Liraglutide + metformin		Dulaglutide + metformin vs. liraglutide + metformin
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
AWARD-6 (subpopulation)					
Mortality					
All-cause mortality	20	(0)	24	0 (0)	NC
Side effects					
AEs (supplementary information)	20	14 (70.0)	24	12 (50.0)	-
SAEs	20	0 (0)	24	2 (8.3)	0.24 [0.01; 4.69]; 0.218
Discontinuation due to AEs	20	0 (0)	24	3 (12.5)	0.17 [0.01; 3.11]; 0.119
Non-severe confirmed symptomatic hypoglycaemic episodes					
PG ≤ 70 mg/dL	No usable data available for the relevant subpopulation[b]				
PG < 54 mg/dL	No usable data available for the relevant subpopulation[b]				
severe hypoglycaemic episodes	No usable data available for the relevant subpopulation[b]				
Pancreatitis acute[c]	20	0 (0)	24	0 (0)	NC

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [23]). In case of 0 events in one study arm, the correction factor 0.5 was used in both study arms for the calculation of effect and CI.
b. For the relevant subpopulation, Module 4 B only presents analyses in which hypoglycaemic episodes that occurred after administration of a rescue medication were not considered. Rescue medication could be administered to treat severe, persistent hyperglycemia, and as subsequent therapy after termination of the study medication.
c. Adjudicated results based on 2 of 3 of the following criteria: 1: abdominal pain typical for pancreatitis acute, 2: three-fold increase in serum amylase and/or serum lipase, and 3: CT or MRI findings.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CT: computed tomography; MRI: magnetic resonance imaging; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculated; PG: plasma glucose; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 15: Results (morbidity, health-related quality of life – RCT, direct comparison: dulaglutide + metformin vs. liraglutide + metformin

Study Outcome category Outcome	Dulaglutide + metformin			Liraglutide + metformin			Dulaglutide + metformin vs. liraglutide + metformin
	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	MD [95% CI]; p-value
AWARD-6 (subpopulation)							
Morbidity							
Health status (EQ-5D VAS)	No usable data available for the relevant subpopulation[b]						
HbA1c (%) (supplementary information)	No usable data available for the relevant subpopulation[b]						
Body weight (kg) (supplementary information)	No data available for the relevant subpopulation						
BMI (kg/m²) (supplementary information)	No data available for the relevant subpopulation						
Health-related quality of life	No data available[c]						

a. Number of patients considered in the analysis for the calculation of the effect estimation.
b. For the relevant subpopulation, Module 4 B only includes analyses from which data accrued after administration of a rescue medication were excluded. Rescue medication could be administered to treat severe, persistent hyperglycaemia, and as subsequent therapy after termination of the study medication.
c. Deviating from the company, which used the instruments APPADL and IW-SP for the outcome category, these instruments were assigned to the outcome category "morbidity". The corresponding outcomes were not included in the benefit assessment (see Section 2.8.3.4.3.2 of the full dossier assessment).

APPADL: Ability to Perform Physical Activities of Daily Living; BMI: body mass index; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; $HbA1_c$: glycosylated haemoglobin A1c; IW-SP: Impact of Weight on Self-Perception; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Based on the available data at most hints, e.g. of an added benefit, can be determined for the relevant subpopulation due to the high risk of bias at study level and the resulting high risk of bias for the results of all included outcomes (see Section 2.4.1.2 and Section 2.4.2.2).

Mortality

All-cause mortality

No deaths occurred in the relevant subpopulation of the AWARD-6 study. This results in no hint of an added benefit of dulaglutide + metformin in comparison with liraglutide + metformin. An added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Health status (EQ-5D VAS)

There were no usable data on the outcome "health status, measured using the EQ-5D VAS", for the relevant subpopulation. This results in no hint of an added benefit of dulaglutide + metformin in comparison with liraglutide + metformin. An added benefit is therefore not proven.

This deviates from the company's assessment, which used the analyses of the EQ-5D VAS for the relevant subpopulation for the assessment of the added benefit of dulaglutide for the outcome "health status". The company derived no added benefit of dulaglutide from the results.

Health-related quality of life

Outcomes suitable to reflect the health-related quality of life were not recorded in the AWARD-6 study (for reasons, see Section 2.8.3.4.3.2 of the full dossier assessment). There is no hint of an added benefit of dulaglutide + metformin in comparison with liraglutide + metformin. An added benefit is therefore not proven.

This deviates from the company's approach, which used results of the Ability to Perform Physical Activities of Daily Living (APPADL) und Impact of Weight on Self-Perception (IW-SP) questionnaires for the outcome category "health-related quality of life". The company derived no added benefit of dulaglutide from the respective results for the relevant subpopulation.

Side effects

SAEs, discontinuation due to AEs and pancreatitis acute

For the outcomes SAEs, discontinuation due to AEs and pancreatitis acute, there were no statistically significant differences between dulaglutide + metformin in comparison with liraglutide + metformin in the relevant subpopulation of the AWARD-6 study. Hence, there was no hint of greater or lesser harm from dulaglutide in comparison with liraglutide for each of these outcomes; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL and PG< 54 mg/dL) and severe hypoglycaemic episodes

For the outcomes "non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL and PG < 54 mg/dL)" and "severe hypoglycaemic episodes", there were no usable data for a comparison of dulaglutide + metformin with liraglutide + metformin for the relevant subpopulation of AWARD-6. This resulted in no hint of greater or lesser harm from dulaglutide in comparison with liraglutide; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company insofar, as the company also derived no added benefit from the results for these outcomes.

2.4.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present benefit assessment (see also Section 2.8.3.4.3.4 of the full dossier assessment):

- age (< 65 years/≥ 65 years)
- sex (female/male)
- country (Czech Republic/Germany/Hungary/Mexico/Poland/Romania/Slovakia/Spain/ United States of America and Puerto Rico)

The subgroup characteristics for the outcome "HbA1c value" were defined a priori for the total population of the AWARD-6 study.

Interaction tests were only performed if at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

In accordance with the methods described above, no relevant effect modification was identified for the present research question. This concurs with the company's assessment.

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below. Thereby, the different outcome categories and effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [24].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of the added benefit at outcome level

The extent of each added benefit at outcome level for the subpopulation of patients with manifest pre-existing cardiovascular disease was estimated from the results presented in Section 2.4.2 (see Table 16).

Table 16: Extent of added benefit at outcome level: dulaglutide + metformin vs. liraglutide + metformin

Outcome category **Outcome**	**Dulaglutide + metformin vs. liraglutide + metformin** **proportion of events (%) or MD** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	0% vs. 0% RR: NC	Lesser benefit/added benefit not proven
Morbidity		
EQ-5D VAS	No usable data	Lesser benefit/added benefit not proven
Health-related quality of life	No data	Lesser benefit/added benefit not proven
Side effects		
SAEs	0% vs. 8.3% RR: 0.24 [0.01; 4.69] p = 0.218	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 12.5% RR: 0.17 [0.01; 3.11] p = 0.119	Greater/lesser harm not proven
Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)	No usable data	Greater/lesser harm not proven
Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)	No usable data	Greater/lesser harm not proven
Severe hypoglycaemic episodes	No usable data	Greater/lesser harm not proven
Pancreatitis acute	0% vs. 0% RR: NC	Greater/lesser harm not proven

a. Probability provided if a statistically significant and relevant effect is present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; NC: Not calculated; PG: plasma glucose; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Relevant data for patients without manifest pre-existing cardiovascular disease are not available.

2.4.3.2 Overall conclusion on added benefit

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit in patients with manifest pre-existing cardiovascular disease.

Table 17: Positive and negative effects from the assessment of dulaglutide + metformin in comparison with liraglutide + metformin in patients with manifest pre-existing cardiovascular disease

Positive effects	Negative effects
-	-

Overall, the assessment revealed neither positive nor negative effects of dulaglutide in comparison with liraglutide.

In summary, an added benefit of dulaglutide + metformin over liraglutide + metformin has not been proven for patients with type 2 diabetes mellitus with manifest pre-existing cardiovascular disease, in whom diet, exercise and treatment with one other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control.

Due to lack of relevant data, an added benefit of dulaglutide versus the ACT has not been proven for dulaglutide in combination with metformin in adults without manifest cardiovascular disease. Due to lack of relevant data, an added benefit of dulaglutide versus the ACT has not been proven for dulaglutide in combination with one other blood-glucose lowering drug (except metformin and insulin).

This is consistent with the company's assessment for dulaglutide in combination with metformin in adults with manifest cardiovascular disease (AWARD-6 study). Moreover, the company derived proof of considerable added benefit of dulaglutide versus the ACT for the patient group with increased cardiovascular risk on the basis of the REWIND study presented by it in Module 4 E of the dossier.

2.5 Research question C: dulaglutide in combination with at least 2 other blood-glucose lowering drugs (except insulin)

2.5.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dulaglutide (status: 18 November 2019)
- bibliographical literature search on dulaglutide (last search on 4 November 2019)
- search in trial registries for studies on dulaglutide (last search on 5 November 2019)

To check the completeness of the study pool:

- search in trial registries for studies on dulaglutide (last search on 14 February 2020)

The check of the completeness of the study pool produced no RCTs on the direct comparison of dulaglutide with the ACT for research question C (dulaglutide in combination with at least 2 other blood-glucose lowering drugs [except insulin]). This assessment concurs with that of the company.

However, the company stated that relevant results for the patient population considered in the present therapeutic indication can be obtained from the REWIND study presented in Module 4 E. This assessment was not appropriate. The REWIND study was not relevant for the assessment of the added benefit of dulaglutide in the present research question. This is particularly due to the fact that REWIND permits no comparison with the ACT specified by the G-BA (see information on the REWIND study in Appendix A of the full dossier assessment).

2.5.2 Results on added benefit

In its dossier, the company presented no relevant data for the assessment of dulaglutide in the combination therapy for adults with type 2 diabetes mellitus in whom diet, exercise and treatment with at least 2 blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control. This resulted in no hint of an added benefit of dulaglutide in comparison with the ACT. An added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

Since no relevant data are available for the assessment of the added benefit of dulaglutide in comparison with the ACT in adults with type 2 diabetes mellitus in whom diet, exercise and treatment with at least two other blood glucose-lowering drugs (except insulin) do not provide adequate glycaemic control, an added benefit of dulaglutide has not been proven for this research question.

This deviates from the company's assessment. Based on the REWIND study presented by it in Module 4 E of the dossier, the company derived considerable added benefit of dulaglutide in comparison with the ACT for patients in research question C who have an increased cardiovascular risk.

2.6 Research question D: dulaglutide in combination with insulin (with or without another blood-glucose lowering drug)

2.6.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dulaglutide (status: 18 November 2019)
- bibliographical literature search on dulaglutide (last search on 4 November 2019)
- search in trial registries for studies on dulaglutide (last search on 5 November 2019)

To check the completeness of the study pool:

- search in trial registries for studies on dulaglutide (last search on 14 February 2020)

The relevant study AWARD-4 was additionally identified from the check. However, the company excluded this study. It justified this with the fact that during the selection it only chose those studies that had not been completely assessed by the G-BA yet in the first assessment of dulaglutide [25] (see Section 2.8.5.2 of the full dossier assessment). This approach was not appropriate. Relating to research question D, the company's dossier is thus incomplete with regard to content.

2.6.1.1 Studies included

Dulaglutide in combination with a short-acting insulin (with or without another blood-glucose lowering drug)

The studies listed in Table 18 are relevant for the combination of dulaglutide with a short-acting insulin (with or without another blood-glucose lowering drug).

Table 18: Study pool – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
H9X-MC-GBDX (AWARD-7)[d]	Yes	Yes	No	Yes [26]	Yes [27-30]	Yes [31,32]
H9X-MC-GBDD (AWARD-4)[d, e]	Yes	Yes	No	Yes [33]	Yes [34-37]	Yes [25,38-41]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA's website.
d. In the following tables, the study is referred to with this abbreviated form.
e. The data on the study category were taken from the first assessment of dulaglutide [25].

CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of dulaglutide in adults with type 2 diabetes mellitus in whom diet, exercise and treatment with insulin (with or without another blood-glucose lowering drug) do not provide adequate glycaemic control, consists of the studies H9X-MC-GBDX (hereinafter referred to as AWARD-7) and H9X-MC-GBDD (hereinafter referred to as AWARD-4).

The study pool differs from that of the company, as the company only included the AWARD-7 study in its assessment. The company excluded AWARD-4 on the grounds that the G-BA had already assessed this study completely in the first assessment of dulaglutide [25] (see Section 2.8.5.2 of the full dossier assessment).

This approach was not appropriate. The results of all studies relevant for the present research question are to be included for the derivation of the added benefit of dulaglutide; a meta-analysis should be considered if several studies are available. This is independent of whether a study has already been evaluated by the G-BA in an early benefit assessment. Relating to research question D, the company's dossier is thus incomplete with regard to content.

Despite this incompleteness of the dossier with regard to content, it is appropriate to assess the AWARD-7 study presented by the company in the dossier without meta-analysis with the AWARD-4 study. This is because, in contrast to the AWARD-4 study, AWARD-7 only investigates a population with moderate or severe renal insufficiency in which a blood glucose target value above the near-normal range was aimed at (see Section 2.6.1.2). Among other things, this resulted in a clearly lower risk of hypoglycaemic episodes compared to AWARD-4. Accordingly, conclusions on the added benefit of dulaglutide can only be made for the subpopulation of patients from AWARD-7 with moderate or severe renal insufficiency in whom no normoglycaemia was aimed at.

Dulaglutide in combination with a long-acting insulin (with or without another blood-glucose lowering drug)

No relevant studies were identified on the combination of dulaglutide with a long-acting insulin (with or without another blood-glucose lowering drugs). This concurs with the company's assessment.

2.6.1.2 Study characteristics

Table 19 and Table 20 describe the study used for the benefit assessment.

Table 19: Characteristics of the study included – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AWARD-7	RCT, open-label[b], parallel	Adults with type 2 diabetes mellitus and moderate or severe CKD[c], ▪ group A[d]: ▫ pretreated with insulin + OAD and/or pramlintide and ▫ HbA1c at screening (week −13): ≥ 7.5% and ≤ 10.5% ▪ group B[e]: ▫ pretreated only with insulin and ▫ HbA1c at screening (week −3): ≥ 7.5% and ≤ 10.5%	Dulaglutide, 0.75 mg/week + insulin lispro (N = 190)[f] dulaglutide, 1.5 mg/week + insulin lispro (N = 193) insulin glargine + insulin lispro (N = 194)	Screening/lead-in: 3 or 13 weeks[g] treatment[h]: 52 weeks follow-up: 4 weeks	99 centers in Brazil, Hungary, Mexico, Poland, Romania, South Africa, Spain, Ukraine and USA 08/2012–12/2016	Primary: change in HbA1c after 26 weeks secondary: mortality, morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Blinding of investigators and patients only with regard to the dulaglutide dosage.
c. Patients with suspected diabetic kidney disease (with or without hypertensive nephrosclerosis) and with diagnosed moderate or severe CKD (corresponds to stage 3 and 4 CKD, defined via an eGFR of < 60 to ≥ 15 mL/min/1.73 m²).
d. In the phase until randomization, group A underwent a lead-in phase of 13 weeks (week −13 to week 0), in which all OADs ± pramlintide were discontinued at week −12. The basic insulin dosage should be optimized within the further lead-in phase. At week −1, the HbA1c value still had to be ≥ 7.5% for patients to be admitted for randomization.
e. For the phase until randomization, group B underwent a lead-in phase of 3 weeks (week −3 to week 0), during which the insulin regime was to remain stable.
f. The arm is not relevant for the present assessment and is not shown in the next tables.
g. Depending on the antidiabetic therapy (group A or B) at screening.
h. From the date of randomization, no distinction was made between group A or B.

AE: adverse event; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HbA1c: glycosylated haemoglobin A1c; N: number of randomized patients; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus

Table 20: Characteristics of the intervention – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro (multipage table)

Study	Intervention	Comparison
AWARD-7	Dulaglutide 1.5 mg, SC, once weekly at the same day of the week and at the same time[a] + insulin lispro, SC, 3 times daily, prandial	Insulin glargin, SC, once daily before bedtime, + insulin lispro, SC, 3 times daily, prandial
	Pretreatment ▪ insulin + OAD and/or pramlintide (group A) or ▪ only insulin at a stable dose[b] for at least 4 weeks before screening (group B) **Lead-in phase** ▪ group A (13 weeks): discontinuation of OAD ± pramlintide and optimization of the insulin regimen by the investigator taking into account the recommendations of the NFK KDOQI guideline ▪ group B (3 weeks): no change in the ongoing insulin regimen	
	Algorithm for the change of insulin administration before randomization to the study treatment	
	Insulin glargine	
	Insulin administration at randomization	Initial treatment dose of insulin glargine (once daily)
	NPH once daily, insulin lente, insulin glargine or insulin detemir	Same number of insulin units
	NPH or insulin lente twice daily	Dose reduction by 20–30% in accordance with the approval of insulin glargine
	Mixed insulin (humulin 70/30, novolog mix 70/30, humalog mix 75/25 or novolin 70/30) once daily	Calculation of the total amount of basal insulin administered and administration of the same number of units
	Mixed insulin (humulin 70/30, novolog mix 70/30, humalog mix 75/25 or novolin 70/30) twice daily	Calculation of the total amount of basal insulin administered and reduction of the dose by 20–30% according to the approval of insulin glargine
	Insulin lispro	
	Insulin administration at randomization	Initial treatment dose of insulin lispro (prandial)
	No prior short-acting or long-acting insulin	3 insulin units with the meals
	Regular human insulin or rapid-acting insulin analogues with the meals	Same number of daily units and distribution according to the number of meals
	Mixed insulin	Calculation of the total amount of short-acting insulin and distribution according to the number of meals

Table 20: Characteristics of the intervention – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro (multipage table)

Study	Intervention	Comparison
	Titration based on target value for insulin glargine and insulin lispro during the study[c]	
	Titration scheme for insulin glargine	
	FPG (mean value of 3 days) [mg/dL]	Dose adjustment of insulin glargine [units]
	< 79	−4
	80–99	−2
	100–150	no changes
	151–170	+2
	171–190	+3
	191–210	+4
	> 210	+5
	Titration scheme for insulin lispro[d]	
	PG (mean value of 3 days[e]) [mg/dL]	Dose adjustment of insulin lispro [units]
	< 89	−2
	90–119	−1
	120–180	no changes
	181–200	+1
	201–220	+2
	> 220	+3
	Concomitant interventions ▪ During the lead-in phase, training was provided (by qualified medical personnel) on nutrition and exercise, measurement and recording of PG levels, injection techniques for the study medication, handling of hypo- and hyperglycaemia, documentation of body weight and blood pressure values and use of the study diary. ▪ Patients were encouraged to follow the corresponding recommendations of the investigator throughout the entire course of the study.	
	Concomitant treatment ACE inhibitors and/or angiotensin receptor blockers[f]	
	Non-permitted concomitant treatment ▪ Insulin except insulin glargine and insulin lispro ▪ OAD (except as rescue medication) and pramlintide ▪ Other GLP-1 receptor agonists (exenatide, liraglutide), DPP-4 inhibitors, metformin ▪ Systemic glucocorticoids > 14 days[g] ▪ Drugs to promote weight loss ▪ The following drugs were to be avoided: ▫ Drugs that alter serum creatinine or reduce eGFR[h] ▫ Drugs with nephrotoxic side effects ▫ NSAID and COX-2 inhibitors[j]	

Table 20: Characteristics of the intervention – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro (multipage table)

Study	Intervention	Comparison
a. Change/adjustment of the dulaglutide dose was not allowed during the course of the study. b. No change of more than 10% in both directions. c. Dose adjustments for insulin glargine and insulin lispro had to be made at least once a week and could be made up to every 3 days. d. Titration of the insulin lispro dose was based on PG values, i.e. on the mean value of PG of the last 3 days. Adjustment for a meal (e.g. breakfast) was based on the mean values of the respective subsequent meal of the day (e.g. before lunch) measured on the preceding 3 days; for the evening meal, adjustment was made on the basis of the mean PG value before bedtime measured on the preceding 3 days . e. Average PG value before lunch, before the evening meal or before going to bed. f. At the time of screening, the patient was to have received an ACE inhibitor and/or an angiotensin receptor antagonist from a physician at the maximum recommended dose. The dosage should have been stable for at least 1 month before screening and was not expected to require adjustment during the trial. Participation in the study was also allowed in cases of intolerance to these drugs. g. Topical, intraocular, intranasal, intrarectal or inhalative applications were allowed. h. Unless they were vital to the patient. i. A switch to paracetamol was to be made instead. ACE: angiotensin converting enzyme; COX-2: cyclooxigenase-2; DPP-4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; GLP-1: glucagon-like peptide 1; NFK KDOQI: National Kidney Foundation Kidney Disease Outcomes Quality Initiative; NPH: neutral protamine Hagedorn; NSAID: nonsteroidal anti-inflammatory drug; OAD: oral antidiabetics; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus		

Study characteristics

AWARD-7 is a 3-arm, randomized, active-controlled, open-label phase 3 study with a treatment duration of 26 (primary treatment phase) or 52 weeks (prolonged treatment phase) which compared a combination therapy of dulaglutide and insulin lispro with a combination therapy of insulin glargine and insulin lispro.

The study included adults with type 2 diabetes mellitus and moderate or severe chronic kidney disease (stage 3 and 4) according to the NFK KDOQI [42] guideline. The stages were defined as eGFR from ≥ 15 to < 60 mL/min/1.73 m².

Depending on their pretreatment, the patients were divided into 2 groups at the time of screening and underwent lead-in phases of various lengths until randomization:

- Group A: Patients pretreated with insulin and an oral antidiabetic and/or pramlintide underwent a 13-week lead-in phase if their HbA1c value was between ≥ 7.5% and ≤ 10.5% at the first visit (week −13, screening visit). In these patients, oral antidiabetics and pramlintide were discontinued at visit 1A (week −12), and the insulin regimen ongoing at the beginning of the lead-in phase was optimized by the investigators according to the specifications of the NFK KDOQI guideline (2007). Patients were included in the study if their HbA1c value was still ≥ 7.5% at the second visit (week −1). This optimization phase in the run-up to the study is relevant to ensure that the treatment effect in the study could not have been achieved by insulin adjustment alone.

- Group B: Patients who had received a stable insulin regimen (no changes of the total daily dose by more than 10%) at least 4 weeks before the start of the study underwent a 3-week lead-in phase and were included in the study if their HbA1c value ranged between ≥ 7.5% and ≤ 10.5% at the first visit (week −3, screening visit). During this phase, insulin regimen and dose were expected to remain stable.

Moreover, at the start of the lead-in phase, patients received counselling (from qualified medical personnel) on nutrition and exercise, measurement and recording of PG levels, injection techniques for the study medication, handling of hypo- and hyperglycaemia, documentation of body weight and blood pressure values and use of the study diary. The patients were encouraged to follow the corresponding recommendations throughout the entire course of the study. Moreover, each patient was also provided with a device for measuring blood glucose and blood pressure and the patients were trained to use these devices.

After randomization (day 0), distinction between group A or B was no longer made, and patients were switched to the study medication (see below).

At the start of the study, 577 patients were randomly assigned to the study arms dulaglutide 0.75 mg/week (N = 190), dulaglutide 1.5 mg/week (N = 193) and insulin glargine (N = 194) in a 1:1:1 ratio, each in combination with insulin lispro. Stratification was made according to the severity of the chronic kidney disease (stage 3a, 3b or 4), macroalbuminuria (yes/no) and region, whereby the characteristics macroalbuminuria and region were combined into the characteristic "macroalbuminuria region" to form a single stratification characteristic.

Primary outcome of the study was the change in HbA1c compared to baseline after 26 weeks of treatment. Patient-relevant secondary outcomes were "all-cause mortality" and outcomes on morbidity and AEs.

Treatment with the study medication

In the AWARD-7 study, treatment with dulaglutide (1.5 mg/week), insulin glargine and insulin lispro was in compliance with the respective SPC [20,43,44]. The study arm "dulaglutide 0.75 mg/week" is not relevant for the assessment, since dulaglutide at this dose is only approved as monotherapy or as an initial dosage in the combination therapy in individuals potentially at risk [20]. Therefore, the study arm is not considered further.

At study start, the patients were switched to the respective study medication (see Table 20). In the intervention arm, the ongoing insulin regimen was discontinued and treatment with dulaglutide and insulin lispro was initiated. The initial dose of insulin lispro was adjusted at the start of the study according to the insulin dose before randomization on the basis of a specified algorithm (see Table 20). Dulaglutide should be injected once weekly at the same time of day and on the same day of the week. The dulaglutide dose was not titrated. In the control arm, patients were switched to initial doses of insulin glargine and insulin lispro according to their pretreatment at randomization on the basis of a specified algorithm (see Table 20). Insulin lispro

was administered 3 times daily with the meals in both study arms. Hence, the treatment regimen administered in the control arm of the study was consistent with an intensified conventional treatment (ICT).

During the study, both the insulin glargine dose in the control arm and the dose of the prandially administered insulin lispro in both study arms was titrated on the basis of the mean fasting plasma glucose (FPG) levels of 3 days (see Table 20). Patients were to measure PG levels before breakfast (for the titration of insulin glargine), before lunch, before dinner and before going to bed on 3 subsequent days prior to the visits. Dose adjustments had to be made at least once weekly, but could be made up to every 3 days. Treatment goals were not specified for the individual patients, but treatment was targeted at an average glucose level of < 154 mg/dL. For this purpose, insulin glargine was titrated to a uniform FPG level of 100 to 150 mg/dL and insulin lispro to a uniform PG level of 120 to 180 mg/dL.

The target value of < 154 mg/dL (8.6 mmol/L) or HbA1c < 7% aimed at in the AWARD-7 study corresponds to the target value recommended as reference values by the NFK KDOQI guideline on diabetes and chronic kidney disease [42] and ranges above the interval of 100 to 125 mg/dL recommended as reference values by the German National Care Guideline (NVL) on the treatment of type 2 diabetes mellitus [45].

After discontinuation or termination of the study medication, the treating physician could choose the antihyperglycaemic treatment regimen for the follow-up observation phase. Treatment with other GLP-1 receptor agonists and DPP-4 inhibitors was excluded.

Patient characteristics

Table 21 shows the characteristics of the patients in the study included.

Table 21: Characteristics of the study population – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro (multipage table)

Study Characteristics Category	**Dulaglutide + insulin lispro N[a] = 183**	**Insulin glargine + insulin lispro N[a] = 186**
AWARD-7		
Age [years], mean (SD)	65 (9)	64 (8)
Sex [F/M], %	45/55	53/47
Family origin, n (%)		
Native American or Alaskan	10 (6)	18 (10)
Asian	7 (4)	5 (3)
Black or African American	23 (13)	25 (14)
Native Hawaiians or other Pacific Islanders	0 (0)	1 (1)
White	131 (73)	130 (70)
Several	9 (5)	6 (3)
Body weight [kg], mean (SD)	88.0 (16.2)	88.1 (18.2)
BMI [kg/m²], mean (SD)	32.0 (4.8)	32.5 (5.3)
Diabetes duration (years) at baseline[b], mean (SD)	17.7 (8.8)	18.6 (8.8)
Duration of the chronic kidney disease stage ≥ 3 (years) at baseline[b], mean (SD)	4.2 (5.7)	3.5 (4.0)
eGFR (CKD-EPI) at baseline[c] (mL/min/1.73 m²), n (%)		
Baseline eGFR ≥ 90	0 (0)	0 (0)
60 ≤ baseline eGFR < 90	8 (4)	13 (7)
45 ≤ baseline eGFR < 60	51 (28)	50 (27)
30 ≤ baseline eGFR < 45	70 (38)	64 (34)
15 ≤ baseline eGFR < 30	52 (28)	58 (31)
Baseline eGFR < 15	2 (1)	1 (1)
eGFR (CKD-EPI) at baseline[c] (mL/min/1.73 m²), mean (SD)	38.0 (13.3)	38.5 (13.0)
UACR[d] at baseline[c] (g/kg), n (%)		
UACR < 30	30 (16)	47 (25)
30 ≤ UACR ≤ 300	73 (40)	55 (30)
UACR > 300	80 (44)	84 (45)
UACR at baseline[c] (g/kg), mean (SD)	756.5 (1294.7)	891.6 (1501.3)
HbA1c (%) at baseline[b], n (%)		
$HbA1_c$ ≤ 8.5	91 (50)	109 (59)
HbA1[c] > 8.5	92 (50)	77 (41)
$HbA1_c$ at baseline[b] (%), mean (SD)	8.6 (0.9)	8.6 (1.0)
Daily total insulin dose (units/kg/day), mean (SD)	0.7 (0.3)	0.7 (0.3)
Prior cardiovascular disease[e], n (%)		
Yes	73 (40)	70 (38)
No	110 (60)	116 (62)
Treatment discontinuation, n (%)	54 (28)	28 (14)
Study discontinuation, n (%)	36 (19)	31 (16)

Table 21: Characteristics of the study population – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro (multipage table)

Study Characteristics Category	Dulaglutide + insulin lispro N[a] = 183	Insulin glargine + insulin lispro N[a] = 186

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Value at visit 3.
c. Mean value of visit 2 and 3.
d. UACR < 30: normal albuminuria; 30 ≤ UACR ≤ 300: microalbuminuria; UACR > 300: macroalbuminuria.
e. Defined as at least one of the following events: myocardial infarction, coronary revascularization, hospitalization due to unstable angina pectoris or due to cardiac insufficiency, stroke or TIA, peripheral arterial occlusive disease, arterial revascularization of the lower limbs or the carotid arteries or documented coronary artery disease.

BMI: body mass index; CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; F: female; $HbA1_c$: glycosylated haemoglobin A1c; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; TIA: transient ischaemic attack; UACR: urine albumin-to-creatinine ratio; vs.: versus

The demographic and clinical characteristics of the patients were largely balanced between the individual study arms.

The mean age of the patients of both study arms was 65 years. The proportion of included men and women was almost equal. The mean HbA1c value at baseline was 8.6% in both study arms. Twice as many patients discontinued the study medication in the intervention arm (28%) than in the comparator arm (14%). The number of patients who discontinued the study was 19% in the intervention arm and 16% in the comparator arm.

Risk of bias across outcomes (study level)

Table 22 shows the risk of bias across outcomes (risk of bias at study level).

Table 22: Risk of bias across outcomes (study level) – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
AWARD-7	Yes	Yes	No	No	Yes	Yes	Low

RCT: randomized controlled trial; vs.: versus

For the AWARD-7 study, the risk of bias across outcomes was rated as low. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described under the outcome-specific risk of bias in Section 2.6.2.2.

2.6.2 Results on added benefit

2.6.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.5.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - ESRD
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - non-severe confirmed symptomatic hypoglycaemic episodes
    - PG < 54 mg/dL
    - PG ≤ 70 mg/dL
  - severe hypoglycaemic episodes
  - pancreatitis acute (adjudicated events)
  - possibly, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 D). Deviating from the company, the outcome "progression to end-stage renal disease" was assigned to the outcome category "morbidity". The outcome "change in HbA1c" and the outcomes "changes in body weight" and "changes in BMI" were presented as supplementary information. An explanation on the inclusion of outcomes can be found in Section 2.8.5.4.3 of the full dossier assessment.

Table 23 shows for which outcomes data were available in the study included.

Table 23: Matrix of outcomes – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro

Study	Outcomes									
	All-cause mortality	Progression to ESRD	Health-related quality of life	SAEs	Discontinuation due to AEs	Pancreatitis acute[a]	Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)	Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)	Severe hypoglycaemic episodes	Gastrointestinal disorders[b]
AWARD-7	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Adjudicated events based on 2 of 3 of the following criteria: 1: abdominal pain typical for pancreatitis acute, 2: Three-fold increase of the upper limit of normal of serum amylase and/or serum lipase and 3: detection by CT or MRI.
b. The following events are considered (MedDRA coding): “gastrointestinal disorders (SOC, AE)”, “diarrhoea (PT, AE)”, “nausea (PT, AE)” and “vomiting (PT, AE)”.
c. The company presented no data on this outcome category.

AE: adverse event; CT: computed tomography; ESRD: end-stage renal disease; MedDRA: Medical Dictionary for Regulatory Activities; MRI: magnetic resonance imaging; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.6.2.2 Risk of bias

Table 24 describes the risk of bias for the results of the relevant outcomes.

Table 24: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro

Study	Study level	Outcomes									
		All-cause mortality	Progression to ESRD	Health-related quality of life	SAEs	Discontinuation due to AEs	Pancreatitis acute[a]	Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)	Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)	Severe hypoglycaemic episodes	Gastrointestinal disorders[b]
AWARD-7	L	H[c]	H[c]	–[d]	H[c]	H[e]	H[c]	H[c]	H[c]	H[c]	H[c, e]

a. Adjudicated events based on 2 of 3 of the following criteria: 1: abdominal pain typical for pancreatitis acute, 2: Three-fold increase of the upper limit of normal of serum amylase and/or serum lipase and 3: detection by CT or MRI.
b. The term summarizes the following outcomes (MedDRA coding): "gastrointestinal disorders (SOC, AE)", "diarrhoea (PT, AE)", "nausea (PT, AE)" and "vomiting (PT, AE)".
c. High (> 10%) or unclear proportion of incomplete observations.
d. The company presented no data on this outcome category.
e. Lack of blinding in subjective recording of outcomes or subjective request for discontinuation.

AE: adverse event; CT: computed tomography; H: high; ESRD: end-stage renal disease; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; SAE: serious adverse event; vs.: versus

For the AWARD-7 study, the risk of bias for the results of all included outcomes was rated as high. Except for the outcome "discontinuation due to AEs", the high risk of bias results from the large or unclear proportion of incomplete observations. For the results of the outcome "gastrointestinal disorders" (SOC, including the corresponding PTs diarrhoea, nausea and vomiting), there is an additional high risk of bias due to the lack of blinding in subjective recording of outcomes. For the results of the outcome "discontinuation due to AEs", the lack of blinding in subjective recording of outcomes is the sole reason for assessing the risk of bias as high.

This assessment deviates from the assessment of the company insofar as the company assessed the risk of bias as low for the results of all outcomes except for "discontinuation due to AEs". For the results of the outcome "discontinuation due to AEs", the risk of bias was also rated as high by the company due to lack of blinding in subjective recording of outcomes. The company did not consider the outcome "gastrointestinal disorders (SOC, including the PTs diarrhoea, nausea and vomiting)" and has thus not assessed the risk of bias. Moreover, the company assigned the outcome "progression to end-stage renal disease" to the outcome category "side

effects". Deviating from the company, this outcome was assigned to the outcome category "morbidity" in the present assessment.

Detailed comments on the risk of bias can be found in Section 2.8.5.4.2 of the present benefit assessment.

2.6.2.3 Results

Table 25 and Table 26 summarize the results on the comparison of dulaglutide with insulin glargine, each in combination with insulin lispro, in patients with type 2 diabetes mellitus in whom diet, exercise and treatment with insulin (with or without another blood-glucose lowering drug) do not provide adequate glycaemic control. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Tables on common AEs, SAEs and discontinuations due to AEs are presented in Appendix C.2 of the full dossier assessment.

Table 25: Results (mortality, morbidity) – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro (multipage table)

Study Outcome category Outcome	Dulaglutide + insulin lispro		Insulin glargine + insulin lispro		Dulaglutide + insulin lispro vs. insulin glargine + insulin lispro
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
AWARD-7					
Mortality					
All-cause mortality	192	3 (1.6)	194	6 (3.1)	0.50 [0.12; 2.04]; 0.324
Morbidity					
Progression to ESRD[b]	192	20 (10.4)	194	27 (13.9)	0.75 [0.43; 1.29]; 0.299[c]
Health-related quality of life					
Outcome not recorded					
Side effects					
AEs (supplementary information)	192	172 (89.6)	194	160 (82.5)	–
SAEs	192	41 (21.4)	194	56 (28.9)	0.74 [0.52; 1.06]; 0.098
Discontinuation due to AEs	192	22 (11.5)[d]	194	7 (3.6)	3.32 [1.45; 7.62]; 0.002
Gastrointestinal disorders (SOC, AE)	192	89 (46.4)	194	46 (23.7)	1.97 [1.47; 2.64]; < 0.001
Diarrhoea (PT, SAE)	192	33 (17.2)	194	14 (7.2)	2.39 [1.32; 4.30]; 0.003
Nausea (PT, AE)	192	38 (19.8)	194	9 (4.6)	4.26 [2.12; 8.53]; < 0.001
Vomiting (PT, AE)	192	26 (13.5)	194	9 (4.6)	2.93 [1.41; 6.05]; 0.002
Non-severe confirmed symptomatic hypoglycaemic episodes					
PG < 54 mg/dL	190[e]	58 (30.5)	194	80 (41.2)	0.74 [0.56; 0.97][c]; 0.029[c]
PG ≤ 70 mg/dL	190[e]	88 (46.3)	194	124 (63.9)	0.72 [0.60; 0.87][c]; < 0.001[c]
Severe hypoglycaemic episodes[f]	190[e]	0 (0)	194	12 (6.2)	0.04 [0.00; 0.68][c]; < 0.001[c]
Pancreatitis acute[g]	192	2 (1.0)	194	1 (0.5)	1.98 [0.20; 19.10][h]; 0.601[c]

a. RR, 95% CI and p-value: Cochran-Mantel-Haenszel method stratified by CKD category at baseline.
b. Includes the following events: stage V CKD, necessity of renal replacement therapy or eGFR < 15 mL/min/1.73 m^2.
c. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, (CSZ method according to [23]). In case of 0 events in one study arm, the correction factor 0.5 was used in both study arms for the calculation of effect and CI.
d. Includes 1 event "sudden death".
e. For 2 patients in the dulaglutide treatment arm who dropped out of the study on the starting day, there were no data on hypoglycaemic episodes after the start of the study. Analogous to the study report, they were excluded from the analysis on hypoglycaemic episodes.
f. The present analysis of the outcome considered no events that had occurred after administration of a rescue medication or after termination of the study medication. However, the study documents show that this applies to at most 1 patient in the dulaglutide arm (see Section 2.8.5.4.3.2 of the full dossier assessment).
g. These are adjudicated events based on two of three of the following criteria: 1: abdominal pain typical for pancreatitis acute, 2: ≥ 3-fold increase of the upper limit of serum amylase and/or serum lipase, and 3: detection by CT or MRI.
h. Peto OR as estimate for RR.

Table 25: Results (mortality, morbidity) – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro (multipage table)

Study Outcome category Outcome	Dulaglutide + insulin lispro		Insulin glargine + insulin lispro		Dulaglutide + insulin lispro vs. insulin glargine + insulin lispro
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
AE: adverse event; CI: confidence interval; CKD: chronic kidney disease; CSZ: convexity, symmetry, z-score; CT: computed tomography; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; n: number of patients with (at least one) event; MRI: magnetic resonance imaging; N: number of analysed patients; OR: odds ratio; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class ; vs.: versus					

Table 26: Results (supplementary outcomes: HbA1c, body weight and BMI) – RCT, direct comparison: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro

Study Outcome category Outcome	Dulaglutide + insulin lispro			Insulin glargine + insulin lispro			Dulaglutide + insulin lispro vs. insulin glargine + insulin lispro
	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)[b]	MD [95% CI]; p-value[b]
AWARD-7							
Morbidity							
HbA1c [%] (supplementary information)	ND	8.60 (0.85)	−0.92 (0.12)	ND	8.56 (0.97)	−0.87 (0.12)	−0.05 [−0.28; 0.17]; ND[c]
Body weight [kg] (additional information)	ND	88.1 (16.01)	−2.27 (0.44)[d]	ND	88.2 (18.49)	1.34 (0.43)[d]	−3.61 [−4.67; −2.55]; < 0.001[d]
BMI (kg/m²)	ND	32.1 (4.84)	−0.82 (0.16)[e]	ND	32.4 (5.33)	0.54 (0.15)[e]	−1.37 [−1.75; −0.98]; < 0.001[e]

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. Unless stated otherwise, MMRM analysis of the mITT population adjusted for treatment, visit, macroalbuminuria region, severity of chronic kidney disease at baseline, HbA1c value and logarithm of the eGFR value at baseline as well as for interaction term for treatment and visit.
c. One-sided p-value is based on tree gatekeeping method for adjustment for multiple testing (p = 0.314).
d. MMRM analysis of the safety population; additionally adjusted for body weight at baseline.
e. MMRM analysis of the safety population; additionally adjusted for BMI at baseline.

BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; HbA1c: glycosylated haemoglobin A1c; ND: no data; MD: mean difference; mITT: modified intention to treat; MMRM: mixed effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Based on the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes due to the high outcome-specific risk of bias.

This deviates from the company's approach, which derived indications, e.g. of an added benefit, for all outcomes.

Mortality

All-cause mortality

Only few deaths occurred in both treatment arms. There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". This resulted in no hint of an added benefit of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Progression to ESRD

No statistically significant difference between the treatment arms was shown for the outcome "progression to end-stage renal disease". This resulted in no hint of an added benefit of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

The dossier contained no data for the outcome category "health-related quality of life". This resulted in no hint of an added benefit of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro for the outcome "health-related quality of life"; an added benefit is therefore not proven.

This deviates from the assessment of the company insofar as the company made no conclusions on the added benefit for the outcome "health-related quality of life" in the dossier.

Side effects

SAEs and pancreatitis acute

There was no statistically significant difference between the treatment arms for the outcomes "SAEs" and "pancreatitis acute". Hence, for these outcomes, there was no hint of greater or lesser harm from dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro was shown for the outcome "discontinuation due to AEs". This resulted in a hint of greater harm from dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro. The events of the outcome "discontinuation due to AEs" are mainly due to gastrointestinal events (see Table 54 of the full dossier assessment).

This concurs with the assessment of the company insofar, as the company also described a statistically significant difference to the disadvantage of dulaglutide in combination with insulin lispro for this outcome. However, deviating from the above result, the company derived an indication.

Gastrointestinal disorders including diarrhoea, nausea and vomiting

There is a statistically significant difference to the disadvantage of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro each for the outcome "gastrointestinal disorders" and the events "diarrhoea", "nausea" and "vomiting" included therein. This resulted in a hint of greater harm from dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro for each the outcome "gastrointestinal disorders" and the events "diarrhoea", "nausea" and "vomiting" included therein.

In its assessment, the company did not consider the outcome "gastrointestinal disorders" with the included events "diarrhoea", "nausea" and "vomiting".

Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL and PG < 54 mg/dL)

A statistically significant difference in favour of dulaglutide + insulin lispro over insulin glargine + insulin lispro was shown for both operationalizations of the outcome "non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL and PG < 54 mg/dL)" and for the outcome "severe hypoglycaemic episodes". In the course of the study, blood-glucose lowering in the intervention arm was comparable to that in the comparator arm (for HbA1c values in the course of the study, see Figure 19 in Appendix C.1 of the full dossier assessment).

However, overall, the effect in non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL) was no more than marginal. Hence, there was no hint of greater or lesser harm from dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro for this outcome; greater or lesser harm is therefore not proven.

Overall, this resulted in one hint of lesser harm from dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro each for non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL) and for the outcome "severe hypoglycaemic episodes".

This concurs with the assessment of the company insofar as the company also described a statistically significant difference in favour of dulaglutide in combination with insulin lispro both for non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL and PG < 54 mg/dL) and severe hypoglycaemic episodes. However, the company only considered analyses in which events that had occurred after administration of a rescue medication were not taken into account (see Section 2.8.5.4.3.2 of the full dossier assessment). Deviating from the result provided above, the company also derived an indication for each of the listed outcomes.

The company additionally considered the outcome "nocturnal hypoglycaemia" and derived an indication of considerable added benefit for dulaglutide versus the ACT. This outcome is not considered separately in the present benefit assessment (for reasons see Section 2.8.5.4.3.2 of the full dossier assessment).

2.6.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present benefit assessment (see also Section 2.8.5.4.3.4 of the full dossier assessment):

- age (< 65 years, ≥ 65 years)
- sex (female/male)
- stage of the chronic kidney disease (3a/3b/4)
- region (OECD country [yes/no])

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

In accordance with the methods described above, no relevant effect modification was identified for the present research question.

2.6.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below. Thereby, the different outcome categories and effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [24].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6.3.1 Assessment of the added benefit at outcome level

Based on the results presented in Section 2.6.2, the extent of the respective added benefit at outcome level is assessed for patients with moderate or chronic kidney disease for whom therapy with a short-acting insulin and blood glucose target values above the near-normal range are aimed at (see Table 27).

Determination of the outcome category for the outcomes on side effects

Information on whether an outcome was serious/severe or non-serious/non-severe is not provided in the dossier for every outcome considered in the present benefit assessment. The classification of these outcomes is justified below.

Discontinuation due to AEs

The events of the outcome "discontinuation due to AEs" were mainly due to gastrointestinal events (see Table 54 of the full dossier assessment). The majority of these events were non-serious/non-severe (see Table 52 and Table 53 of the full dossier assessment). However, overall it is unclear which gastrointestinal events (non-serious/non-severe or serious/severe) have been considered in the outcome "discontinuation due to AEs". There is no further information on the assignment of the severity category for the outcome "discontinuation due to AEs". Therefore, the outcome "discontinuation due to AEs" was assigned to the category "non-serious/non-severe side effects".

Gastrointestinal disorders (including diarrhoea, nausea and vomiting)

Most of the events that occurred in the outcome "gastrointestinal disorders (including diarrhoea, nausea and vomiting)" were non-serious/non-severe. Therefore, the cited outcomes were assigned to the category "non-serious/non-severe side effects".

Table 27: Extent of added benefit at outcome level: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro (multipage table)

Outcome category **Outcome**	**Dulaglutide + insulin lispro vs. insulin glargine + insulin lispro** **proportion of events (%)** **effect estimation [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	1.6% vs. 3.1% RR: 0.50 [0.12; 2.04] p = 0.324	Lesser benefit/added benefit not proven
Morbidity		
Progression to end-stage renal disease	10.4% vs. 13.9% RR: 0.75 [0.43; 1.29] p = 0.299	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcomes of this outcome category were not recorded		
Side effects		
SAEs	21.4% vs. 28.9% RR: 0.74 [0.52; 1.06] p = 0.098	Greater/lesser harm not proven
Discontinuation due to AEs	11.5% vs. 3.6% RR: 3.32 [1.45; 7.62] RR: 0.30 [0.13; 0.69][c] p = 0.002 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Gastrointestinal disorders (AE, SOC)	46.4% vs. 23.7% RR: 1.97 [1.47; 2.64] RR: 0.51 [0.38; 0.68][c] p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Diarrhoea (AE, PT)	17.2% vs. 7.2% RR: 2.39 [1.32; 4.30] RR: 0.42 [0.23; 0.76][c] p = 0.003 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Nausea (AE, PT)	19.8% vs. 4.6% RR: 4.26 [2.12; 8.53] RR: 0.23 [0.12; 0.47][c] p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”

Table 27: Extent of added benefit at outcome level: dulaglutide + insulin lispro vs. insulin glargine + insulin lispro (multipage table)

Outcome category **Outcome**	**Dulaglutide + insulin lispro vs. insulin glargine + insulin lispro** **proportion of events (%)** **effect estimation [95% CI]** **p-value** **probability[a]**	**Derivation of extent[b]**
Vomiting (AE, PT)	13.5% vs. 4.6% RR: 2.93 [1.41; 6.05] RR: 0.34 [0.17; 0.71][c] p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Non-severe confirmed symptomatic hypoglycaemic episodes		
PG < 54 mg/dL	30.5% vs. 41.2% RR: 0.74 [0.56; 0.97] p = 0.029	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[d]
PG ≤ 70 mg/dL	46.3% vs. 63.9% RR: 0.72 [0.60; 0.87] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
severe hypoglycaemic episodes	0% vs. 6.2% RR: 0.04 [0.00; 0.68] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Pancreatitis acute	1.0% vs. 0.5% POR: 1.98 [0.20; 19.10] p = 0.601	Greater/lesser harm not proven

a. Probability provided if a statistically significant and relevant effect is present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; PG: plasma glucose; POR: Peto Odds Ratio; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

No relevant data are available for patients in whom therapy with a short-acting insulin and target blood glucose levels in the near-normal range are aimed at.

2.6.3.2 Overall conclusion on added benefit

Dulaglutide in combination with a short-acting insulin (with or without another blood-glucose lowering drug)

Patient population with target blood glucose levels above the near-normal range (AWARD-7 study)

Concurring with the company, the results of the AWARD-7 study are used to derive the added benefit for the combination of dulaglutide with a short-acting insulin (with or without another blood glucose-lowering drug) and target blood glucose levels above the near-normal range.

Table 28 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 28: Positive and negative effects from the assessment of dulaglutide + insulin lispro in comparison with insulin glargine + insulin lispro

Positive effects	**Negative effects**
Serious/severe side effects ▪ severe hypoglycaemic episodes: hint of lesser harm – extent: "major"	–
Non-serious/non-severe side effects ▪ non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL): hints of lesser harm – extent: "minor"	Non-serious/non-severe side effects ▪ discontinuation due to AEs[a]: hint of greater harm – extent: "considerable" ▪ gastrointestinal disorders (SOC, AE), including diarrhoea (PT, AE), nausea (PT, AE) and vomiting (PT, AE)[a]: hint of greater harm for each of these outcomes – extent: "considerable"
a. The treatment discontinuations were mainly due to gastrointestinal events. AEs: adverse events; PG: plasma glucose; PT: Preferred Term; SOC: System Organ Class	

The overall consideration showed both positive and negative effects of dulaglutide + insulin lispro versus insulin glargine + insulin lispro, each with the same certainty of results ("hint"). However, in summary, the positive effects, which are particularly shown by the hint of lesser harm in the outcome "severe hypoglycaemic episodes" with the extent "major" (outcome category "serious/severe side effects"), outweighed the negative ones.

Overall, this resulted in a hint of considerable added benefit of dulaglutide over insulin glargine, each in combination with insulin lispro, for patients with type 2 diabetes mellitus in whom diet, exercise and treatment with insulin (with or without another blood-glucose lowering drug) do not provide adequate glycaemic control. However, the added benefit only applies to patients for whom treatment with a short-acting insulin and target blood glucose levels above the near-normal range are aimed at.

This deviates from the company's assessment, which derived an indication of considerable added benefit of dulaglutide for patients with type 2 diabetes mellitus and moderate to severe chronic kidney disease. On the basis of the REWIND study presented by it in Module 4 E of the dossier, the company also derived considerable added benefit of dulaglutide versus the ACT for research question D for patients with an increased cardivoascular risk.

Patient population with the treatment goal of near-normal blood-glucose levels (AWARD-4 study)

For the combination of dulaglutide with a short-acting insulin (with or without another blood-glucose lowering drug) and the treatment goal of near-normal blood-glucose levels, the dossier is incomplete in terms of content (for reasons, see Section 2.6.1.1).

Overall, this resulted in no proof of an added benefit of dulaglutide + a short-acting insulin (with or without another blood glucose-lowering drug) and the treatment goal of near-normal blood-glucose levels in comparison with the ACT "optimization of the human insulin regimen" (see Table 29).

Dulaglutide in combination with a long-acting insulin (with or without another blood-glucose lowering drug)

The company presented no data on the combination of dulaglutide with a long-acting insulin (with or without another blood-glucose lowering drug).

Overall, this resulted in no proof of an added benefit of dulaglutide + a long-acting insulin (with or without another blood-glucose lowering drug) versus the ACT "optimization of the human insulin regimen" (see Table 29).

2.7 Probability and extent of added benefit – Summary

The result of the assessment of the added benefit of dulaglutide in comparison with the ACT is summarized in Table 29.

Table 29: Dulaglutide – probability and extent of the added benefit in type 2 diabetes mellitus in adults

Research question	**Subindication[a]**	**ACT[b]**	**Probability and extent of added benefit**
A	Monotherapy in adults in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is unsuitable due to intolerance or contraindications.	▪ Sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Combination therapy in adults in whom diet, exercise and treatment with one other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control	▪ Metformin + sulfonylurea (glibenclamide or glimepiride) or ▪ metformin + empagliflozin or ▪ **metformin + liraglutide[c]** or ▪ human insulin[d]	Added benefit not proven
C	Combination therapy in adults in whom diet, exercise and treatment with at least 2 blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control	▪ Human insulin + metformin or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ human insulin[e]	Added benefit not proven
D	Combination therapy in adults in whom diet, exercise and treatment with a short-acting insulin (with or without other blood-glucose lowering drugs) do not provide adequate glycaemic control	▪ Optimization of the human insulin regimen (if required + metformin or empagliflozin[c] or liraglutide[c])	*Treatment goal near-normal blood glucose levels:* added benefit not proven
			Treatment goal non near-normal blood glucose levels[f]: hint of a considerable added benefit
	Combination therapy in adults in whom diet, exercise and treatment with a long-acting insulin (with or without another blood-glucose lowering drug) do not provide adequate glyceamic control		Added benefit not proven

a. Subdivision of the subindication according to the G-BA.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of the cardiovascular risk factors, particularly antihypertensive agents, anticoagulants and/or lipid-lowering drugs (for operationalization, see study protocols of the relevant studies on empagliflozin [3] and liraglutide [4]).
d. If metformin is not tolerated or contraindicated according to the SPC.
e. If, according to the SPC, metformin and empagliflozin[c] or liraglutide[c] are not tolerated or contraindicated or are not sufficiently effective due to advanced type 2 diabetes mellitus.
f. Therapy targeted at a uniform mean FPG level < 154 mg/dL (100 to 150 mg/dL for insulin glargine or 120 to 180 mg/dL for insulin lispro).

Table 29: Dulaglutide – probability and extent of the added benefit in type 2 diabetes mellitus in adults

Research question	**Subindication[a]**	**ACT[b]**	**Probability and extent of added benefit**
ACT: appropriate comparator therapy; FPG: fasting plasma glucose; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics			

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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