# Dulaglutide
# (type 2 diabetes in children and adolescents)

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

**EXTRACT**

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# Part I: Benefit assessment

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

# I List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| ADA | American Diabetes Association |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| HbA1c | glycated haemoglobin |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |

## I 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 assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 March 2023.

### Research question

The aim of this report was to assess the added benefit of dulaglutide as an adjunct to diet and exercise in the treatment of children and adolescents 10 to 17 years of age with inadequately controlled type 2 diabetes mellitus in comparison with the appropriate comparator therapy (ACT).

The research questions shown in Table 2 were derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of dulaglutide

| Research question | Therapeutic indication | ACT[a] |
|---|---|---|
| 1 | Insulin-naive children and adolescents aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous drug therapy consisting of at least one blood glucose-lowering drug[b] in addition to diet and exercise | Human insulin + metformin[c] |
| 2 | Insulin-experienced children and adolescents aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise | Escalation of insulin therapy (conventional insulin therapy [CT], possibly + metformin or intensified conventional insulin therapy [ICT])[c,d,e] |

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, metformin is the treatment of first choice for drug therapy of type 2 diabetes mellitus in children and adolescents.
c. It is presumed that contraindications for metformin - examples of which as per the Summary of Product Characteristics (SPC) include kidney disease, metabolic acidosis, diabetic precoma, or liver failure - are less commonly observed in children and adolescents. Compared with the total population, a smaller percentage of children and adolescents are presumably contraindicated or intolerant to metformin, even when administered at low dosages. Therefore, no separate patient population with metformin contraindication or intolerance was established. Treatment with insulin is indicated, if necessary in combination with metformin, in case of signs of ketoacidosis or ketonuria, inadequate blood glucose control under metformin therapy, or in very advanced stages of disease. Where treatment escalation options are still available, continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus is not an ACT. In both study arms, potential comorbidities or risk factors for type 2 diabetes mellitus (e.g. hypertension, dyslipidaemia, microvascular complications – nephropathy, neuropathy, retinopathy) were presumably treated in an individualized manner according to the latest medical knowledge, using in particular antihypertensives and/or lipid-lowering drugs.
d. Insulin therapy should be escalated in the form of conventional therapy (CT, mixed insulin) or intensified conventional therapy (ICT), taking into account the patient's individual life situation. In ICT, the administration of an additional blood glucose-lowering drug is not typically deemed indicated. In addition to CT, metformin may be administered if necessary.
e. According to the G-BA, single-comparator studies are typically inadequate for implementing the ACT in a direct comparative study. The investigator is expected to have a choice between several treatment options (CT or ICT) (multi-comparator study). The choice and, if necessary, limitation of treatment options must be substantiated.

ACT: appropriate comparator therapy; CT: conventional insulin therapy; G-BA: Federal Joint Committee; ICT: intensified conventional insulin therapy

The company deviates from the G-BA's specification of the 2 patient populations as well as of the ACT. The company's justifications for these deviations were not followed. The present assessment is therefore carried out for all the patient populations specified by the G-BA in comparison with the respective ACTs.

The assessment is 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 deriving added benefit.

**Deviation from the specified patient population and ACT**

The company followed neither the G-BA's specifications regarding the categorization of the therapeutic indication into 2 patient populations nor the defined ACT. To justify its approach, the company cites the generally limited treatment options for children and adolescents with diabetes mellitus type 2, concluding that the comparator therapy should be extended to all approved options (liraglutide, dapagliflozin, and exenatide) in addition to metformin and insulin. Regarding the extension of the ACT, the company refers to various guidelines and studies. From the company's point of view, the treating physician thus has a broad selection of individualized treatment options at his or her disposal. In the company's view, the present patient population therefore does not need to be split into 2 subpopulations.

The company's approach is not appropriate. A limited selection of approved treatment options does not represent sufficient grounds for departing from the patient populations and ACT specified by the G-BA. Further, the sources provided by the company are insufficient for deriving an ACT. Overall, the company's arguments are unsuitable for justifying a departure from the ACT specified by the G-BA.

**Results**

The check for completeness of the study pool revealed no relevant studies comparing dulaglutide versus the ACT specified by the G-BA for research question 1 nor for research question 2.

The company likewise did not identify a relevant study, but it did present the AWARD-PEDS study for supplementary information.

The AWARD-PEDS study submitted by the company is not suitable for deriving an added benefit of dulaglutide compared to the ACT because it neither presents separate analyses for the patient populations specified by the G-BA nor implements the respective ACT.

**Results on added benefit**

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of dulaglutide in comparison with the ACT; an added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of added benefit[3] of dulaglutide.

[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 [13,14].

Table 3: Dulaglutide – probability and extent of added benefit

| **Research question** | **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|---|
| 1 | Insulin-naive children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous drug therapy consisting of at least one blood glucose-lowering drug[b] in addition to diet and exercise | Human insulin + metformin[c] | Added benefit not proven |
| 2 | Insulin-experienced children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise | Escalation of insulin therapy (conventional insulin therapy [CT], possibly + metformin or intensified conventional insulin therapy [ICT])[c,d,e] | Added benefit not proven |

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, metformin is the treatment of first choice for the drug therapy of type 2 diabetes mellitus in children and adolescents.
c. It is presumed that contraindications for metformin - examples of which as per the Summary of Product Characteristics (SPC) include kidney disease, metabolic acidosis, diabetic precoma, or liver failure - are less commonly observed in children and adolescents. Compared with the total population, a smaller percentage of children and adolescents are presumably contraindicated or intolerant to metformin, even when administered at low dosages. Therefore, no separate patient population with metformin contraindication or intolerance was established. Treatment with insulin is indicated, if necessary in combination with metformin, in case of signs of ketoacidosis or ketonuria, inadequate blood glucose control under metformin therapy, or in very advanced stages of disease. Where treatment escalation options are still available, continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus is not an ACT. In both study arms, it is assumed that treatment of potential comorbidities or risk factors associated with type 2 diabetes such as hypertension, dyslipidemia, and microvascular complications (including nephropathy, neuropathy, and retinopathy), will be individualized and aligned with the latest medical knowledge, primarily using antihypertensive and/or lipid-lowering drugs.
d. Here, insulin therapy should be escalated in the form of conventional therapy (CT, mixed insulin) or intensified convention therapy (ICT), taking into account the patient's individual life situation. In ICT, the administration of an additional blood glucose-lowering drug is not typically deemed indicated. In addition to CT, metformin may be administered if necessary.
e. According to the G-BA, single-comparator studies are typically inadequate for implementing the ACT in a direct comparative study. The investigator is expected to have a choice between several treatment options (CT or ICT) (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.

ACT: appropriate comparator therapy; CT: conventional insulin therapy; G-BA: Federal Joint Committee; ICT: intensified conventional insulin therapy

The G-BA decides on the added benefit.

## I 2 Research question

The aim of this report was to assess the added benefit of dulaglutide as an adjunct to diet and exercise in the treatment of children and adolescents 10 to 17 years of age with inadequately controlled type 2 diabetes mellitus in comparison with the ACT.

The research questions shown in Table 4 were derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of dulaglutide

| Research question | Therapeutic indication | ACT[a] |
|---|---|---|
| 1 | Insulin-naive children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous drug therapy consisting of at least one blood glucose-lowering drug[b] in addition to diet and exercise | Human insulin + metformin[c] |
| 2 | Insulin-experienced children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise | Escalation of insulin therapy (conventional insulin therapy [CT], possibly + metformin or intensified conventional insulin therapy [ICT])[c,d,e] |

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, metformin is the treatment of first choice for the drug therapy of type 2 diabetes mellitus in children and adolescents.
c. Metformin contraindications, which as per metformin SPC include, for example, severe kidney disease, metabolic acidoses, diabetic precoma, or liver failure, are presumably found less frequently in children and adolescents. Compared with the total population, a smaller percentage of children and adolescents are presumably contraindicated or intolerant to metformin, even when administered at low dosages. Therefore, no separate patient population with metformin contraindication or intolerance was established. Treatment with insulin is indicated, if necessary in combination with metformin, in case of signs of ketoacidosis or ketonuria, inadequate blood glucose control under metformin therapy, or in very advanced stages of disease. Where treatment escalation options are still available, continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus is not an ACT. In both study arms, potential comorbidities or risk factors for type 2 diabetes mellitus (e.g. hypertension, dyslipidaemia, microvascular complications – nephropathy, neuropathy, retinopathy) were presumably treated in an individualized manner according to the latest medical knowledge, using in particular antihypertensives and/or lipid-lowering drugs.
d. Insulin therapy should be escalated in the form of conventional therapy (CT, mixed insulin) or intensified conventional therapy (ICT), taking into account the patient's individual life situation. In ICT, the administration of an additional blood glucose-lowering drug is not typically deemed indicated. In addition to CT, metformin may be administered if necessary.
e. According to the G-BA, single-comparator studies are typically inadequate for implementing the ACT in a direct comparative study. The investigator is expected to have a choice between several treatment options (CT or ICT) (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.

ACT: appropriate comparator therapy; CT: conventional insulin therapy; G-BA: Federal Joint Committee; ICT: intensified conventional insulin therapy

The company deviates from the G-BA's specification of the 2 patient populations as well as of the ACT. The company's justifications for these deviations were not followed. The present

assessment is therefore carried out for all the patient populations specified by the G-BA in comparison with the respective ACTs.

The assessment is 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 added benefit.

**Deviation from the specified patient population and ACT**

The company followed neither the G-BA's specifications regarding the categorization of the therapeutic indication into 2 patient populations nor the defined ACT. To justify its approach, the company cites the generally limited treatment options for children and adolescents with diabetes mellitus type 2, concluding that the comparator therapy should be extended to all approved options (liraglutide, dapagliflozin, and exenatide) in addition to metformin and insulin. From the company's point of view, the treating physician thus has a broad selection of individualized treatment options at his or her disposal. In the company's view, the present patient population therefore does not need to be split into 2 subpopulations.

For the extension of the ACT, the company refers to the guideline issued by the American Diabetes Association (ADA) in 2021 [1] and the comments of the professional societies for the specification of the ACT [2], which, in the company's understanding, recommend liraglutide in cases of intolerance or contraindication to metformin or insufficient glycaemic control under metformin (with or without insulin). The company further believes that the updated practice guideline of the German Diabetes Society [3] recommends incretin mimetics and thus liraglutide and exenatide as an alternative or supplement to metformin. Additionally, the company cites 1 study for each of the 3 drugs in which they are investigated in comparison with placebo, typically in addition to standard therapy with metformin (with or without insulin) [4-6].

The approach of the company is not appropriate. A limited selection of approved treatment options does not represent sufficient grounds for departing from the patient populations and ACT specified by the G-BA. Further, the sources provided by the company are insufficient for deriving an ACT. The drugs dapagliflozin and exenatide are not mentioned in the ADA guideline cited by the company [1]. Furthermore, the statements on the use of the drugs liraglutide, dapagliflozin and exenatide made in other national and international guidelines [3,7] [8-10] are not consistent enough as to justify the deviation from the ACT specified by the G-BA. Overall, the company's arguments are unsuitable for justifying a departure from the ACT specified by the G-BA.

## I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dulaglutide (status: 16 January 2023)
- bibliographical literature search on dulaglutide (last search on 16 January 2023)
- search in trial registries/trial results databases for studies on dulaglutide (last search on 18 January 2023)
- search on the G-BA website for dulaglutide (16 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on dulaglutide (last search on 11 April 2023); for search strategies, see Appendix I A of the full dossier assessment

For both research question 1 and research question 2, the check of the completeness of the study pool produced no relevant studies on the comparison of dulaglutide versus the ACT specified by the G-BA for children and adolescents 10 to 17 years of age with type 2 diabetes mellitus.

The company deviates from the ACT specified by the G-BA but does not identify any relevant study, even compared to the comparator therapy chosen by the company itself (see Section I 2).

For supplementary information, the company submits the study H9X-MC-GBGC/AWARD-PEDS (hereafter AWARD-PEDS) [11]. Said study is unsuitable for the derivation of an added benefit of dulaglutide in comparison with the ACT. The rationale is provided below.

**Description of the AWARD-PEDS study**

The AWARD-PEDS study is a 3-arm, multicentre RCT consisting of a double-blind phase and an open-label extension phase of 26 weeks each. The aim of the study was to compare dulaglutide (in 2 different dosing regimens) versus placebo in patients aged 10 to 17 years with type 2 diabetes mellitus who had insufficient blood glucose control despite diet and exercise, with or without metformin and/or basal insulin.

It enrolled patients with a glycated haemoglobin (HbA1c) value > 6.5% and ≤ 11.0%. However, these values did not apply to patients with newly diagnosed disease which had previously been treated with diet and exercise only. In this case, the HbA1c value was to be > 6.5% and ≤ 9.0%.

Drug treatment of diabetes mellitus type 2 at baseline was not an inclusion criterion. Any drug treatment with metformin and/or basal insulin which existed at the time of randomization had to have been at a stable dose for at least 8 weeks prior to screening, with the daily metformin dose being ≥ 1000 mg.

A total of 154 children and adolescents were randomly assigned in a 1:1:1 ratio to 1 of the following 3 treatment arms: (a) 0.75 mg once weekly dulaglutide, (b) 0.75 mg once weekly dulaglutide for 4 weeks with subsequent dose increase to 1.5 mg once weekly – if the previous 0.75 mg dose was well tolerated in the investigator's opinion – or (c) placebo.

It should be noted that the dulaglutide administration in the study deviates from the SPC in both dulaglutide arms. According to the SPC [12], the initial dose for children and adolescents aged 10 to 17 years is 0.75 mg once weekly. If necessary, the dose can be increased after at least 4 weeks to a maximum dose of 1.5 mg once weekly. In arm (a), however, a dose increase to 1.5 mg once weekly was disallowed. In arm (b), the dose was increased to 1.5 mg once weekly, but this increase was not on an as-needed basis, but for all participants at a pre-specified time (Week 4), provided there were no safety concerns.

During the 26-week double-blind treatment phase, the metformin dose was to remain stable, and the basal insulin dose was not to be increased by more than 15% of the existing dose at randomisation. Dose adjustments or treatment escalations of the concomitant antidiabetic therapy were permitted, e.g. in case of the occurrence of hypoglycaemia or hyperglycaemia. If hyperglycaemia persisted (based on fasting plasma glucose values), all treatment arms offered the option of rescue therapy. This was at the investigator’s discretion.

The change in HbA1c value was the primary outcome of the AWARD-PEDS study. Other outcomes included change in fasting plasma glucose levels and body mass index as well as side effects.

**Failure of AWARD-PEDS study to implement the G-BA’s specifications regarding patient population and ACT**

For the AWARD-PEDS study, the company did not submit any analyses for the patient populations specified by the G-BA. Instead, the company’s dossier examined only 1 research question under which it jointly analysed all patients in the present therapeutic indication. Hence, the company’s dossier does not allow assessing the added benefit of dulaglutide versus the ACT for the 2 research questions specified by the G-BA.

In addition, the treatment carried out in the AWARD-PEDS study does not correspond to the ACT specified by the G-BA for the majority of the patients included. For instance, 63% of patients in the placebo arm were initially treated for diabetes using metformin monotherapy

only. Metformin monotherapy is not an ACT specified by the G-BA for the present therapeutic indication, however.

The G-BA notes that continuation of insufficient treatment of type 2 diabetes mellitus does not constitute an ACT as long as options to escalate treatment are still available. Since the patients in the placebo arm had a mean HbA1c value of approx. 8.1% at study start, it can be assumed that, as per guideline recommendations (see e.g. [7,9]), an escalation of therapy to lower the HbA1c value would have been indicated and possible (e.g. by adding insulin) for the majority of patients in the placebo arm. Thus, the lack of optimisation of the existing therapy at the time of randomisation in the placebo arm means that the ACT specified by the G-BA has not been implemented.

The above-described options for therapy escalation in the study do not lead to implementation of the ACT, as they do not correspond to guideline-compliant therapy optimisation.

In summary, the AWARD-PEDS study submitted by the company as supplementary information is not suitable for deriving an added benefit of dulaglutide compared to the ACT because no separate analyses for the patient populations defined by the G-BA are presented, nor was the respective ACT implemented.

## I 4 Results on added benefit

No suitable data are available for assessing the added benefit of dulaglutide in comparison with the ACT, neither for research question 1 (insulin-naive children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous drug treatment consisting of at least 1 blood glucose-lowering drug in addition to diet and exercise) nor for research question 2 (insulin-experienced children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise). This results in no hint of an added benefit of dulaglutide in comparison with the ACT for either of them; an added benefit is therefore not proven.

## I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for dulaglutide in comparison with the ACT.

Table 5: Dulaglutide – probability and extent of added benefit

| Research question | Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| 1 | Insulin-naive children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous drug therapy consisting of at least one blood glucose-lowering drug[b] in addition to diet and exercise | Human insulin + metformin[c] | Added benefit not proven |
| 2 | Insulin-experienced children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise | Escalation of insulin therapy (conventional insulin therapy [CT], possibly + metformin or intensified conventional insulin therapy [ICT])[c,d,e] | Added benefit not proven |

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, metformin is the treatment of first choice for the drug therapy of type 2 diabetes mellitus in children and adolescents.
c. Metformin contraindications, which as per metformin SPC include, for example, severe kidney disease, metabolic acidoses, diabetic precoma, or liver failure, are presumably found less frequently in children and adolescents. Compared with the total population, a smaller percentage of children and adolescents are presumably contraindicated or intolerant to metformin, even when administered at low dosages. Therefore, no separate patient population with metformin contraindication or intolerance was established. Treatment with insulin is indicated, if necessary in combination with metformin, in case of signs of ketoacidosis or ketonuria, inadequate blood glucose control under metformin therapy, or in very advanced stages of disease. Where treatment escalation options are still available, continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus is not an ACT. In both study arms, potential comorbidities or risk factors for type 2 diabetes mellitus (e.g. hypertension, dyslipidaemia, microvascular complications – nephropathy, neuropathy, retinopathy) were presumably treated in an individualized manner according to the latest medical knowledge, using in particular antihypertensives and/or lipid-lowering drugs.
d. Here, insulin therapy should be escalated in the form of conventional therapy (CT, mixed insulin) or intensified convention therapy (ICT), taking into account the patient's individual life situation. In ICT, the administration of an additional blood glucose-lowering drug is not typically deemed indicated. In addition to CT, metformin may be administered if necessary.
e. According to the G-BA, single-comparator studies are typically inadequate for implementing the ACT in a direct comparative study. The investigator is expected to have a choice between several treatment options (CT or ICT) (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.

ACT: appropriate comparator therapy; CT: conventional insulin therapy; G-BA: Federal Joint Committee; ICT: intensified conventional insulin therapy

The assessment described above concurs with that of the company.

The G-BA decides on the added benefit.

## I 6 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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