Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Dulaglutide (new therapeutic indication: type 2 diabetes mellitus, ≥ 10 years)

of 21 September 2023

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient dulaglutide (Trulicity) was listed for the first time on 1 February 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 6 March 2023, dulaglutide received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 31 March 2023 , the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules

of Procedure (VerfO) of the G-BA on the active ingredient dulaglutide with the new therapeutic indication (type 2 diabetes mellitus, ≥ 10 years).

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on the G-BA website (www.g-ba.de) on 3 July 2023, thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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

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

2.1.1 Approved therapeutic indication of Dulaglutide (Trulicity) in accordance with the product information

Trulicity is indicated for the treatment of patients 10 years and above with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin is considered unsuitable due to intolerance or contraindications.
- in addition to other medicinal products for the treatment of diabetes.

Therapeutic indication of the resolution (resolution of 21.09.2023):

For the treatment of children and adolescents aged 10 to 17 years with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin is considered unsuitable due to intolerance or contraindications.
- in addition to other medicinal products for the treatment of diabetes.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children and adolescents aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least one hypoglycaemic agent in addition to diet and exercise

Appropriate comparator therapy for dulaglutide

- A patient-individual therapy, taking into account the HbA1c value, previous therapies and complications with selection of
  - metformin + human insulin
  - metformin + liraglutide
  - an escalation of insulin therapy (conventional therapy (CT) if necessary + metformin or intensified insulin therapy (ICT)).

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

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

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be

assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. Apart from dulaglutide, the active ingredient metformin, the GLP-1 receptor antagonists liraglutide and exenatide, the SGLT-2 inhibitor dapagliflozin and insulin (human insulin, insulin analogues) have been approved so far for the treatment of type 2 diabetes mellitus in children and adolescents 10 years and older.

on 2. A non-medicinal treatment cannot be considered as a comparator therapy in this therapeutic indication.

on 3. For children and adolescents with type 2 diabetes mellitus, there are two resolutions on the benefit assessment according to Section 35 SGB V, for insulin degludec dated 20 August 2015 and for dapagliflozin dated 16 June 2022.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the “Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V”.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

The currently available evidence for the treatment of type 2 diabetes mellitus in children and adolescents is limited overall. Three guidelines were considered, including one from the UK National Institute for Health and Care Excellence (NICE), one from the American Diabetes Association (ADA) and one from the Australasian Paediatric Endocrine Group (APEG). According to the recommendations, metformin is the first choice for the treatment of children and adolescents with type 2 diabetes mellitus. In addition to metformin, the guidelines recommend insulin in combination with metformin as initial therapy in case of signs of ketoacidosis or ketonuria, inadequate glycaemic control under metformin therapy or severe hyperglycaemia in a very extensive-stage of the disease.

It is assumed that metformin contraindications, which according to the product information of metformin exist, for example in severe renal failure, metabolic acidoses, diabetic precoma or liver failure, occur less frequently in children and adolescents.
Metformin intolerances, for example gastrointestinal intolerances can also occur in children and adolescents with type 2 diabetes mellitus, especially at the start of treatment. Clinical experience shows that metformin intolerance occurs with a comparable frequency in children and adolescents with type 2 diabetes mellitus as in adult patients. According to the product information of metformin for use in children and adolescents, a gradual increase in the dosage has a positive effect on the gastrointestinal tolerability of metformin.
Overall, it is therefore assumed that only a smaller percentage of children and adolescents have a metformin contraindication or permanent intolerance compared to the total population.

With the active ingredients exenatide, dapagliflozin and liraglutide, additional treatment options are available for the treatment of children and adolescents 10 years and older with type 2 diabetes mellitus.

According to the guideline of the American Diabetes Association (ADA) the use of a GLP1 agonist in addition to insulin may be considered if there is an inadequate response to metformin. However, there are no recommendations for treatment with the SGLT-2 inhibitor dapagliflozin.

Within the framework of the written statement procedure, it became clear that the therapy of type 2 diabetes mellitus in children and adolescents does not represent a static therapy concept. Rather, the medication should be reviewed regularly and adjusted patient-individually. Thus, the occurrence of metabolic crises (e.g. Ketoacidosis) requires the intake of insulin. However, especially for children and adolescents, one therapeutic goal is to keep the period of insulin intake as short as possible. The administration of insulin in children and adolescents is usually not a long-term therapy and should be replaced by other treatment options, if possible.

If neither treatment with metformin + insulin nor with metformin + liraglutide leads to a sufficient therapeutic response, escalation of insulin therapy is recommended. The escalation of the insulin therapy should take place in the form of a conventional insulin therapy (CT, mixed insulin, if necessary + metformin) or an intensified conventional insulin therapy (ICT), taking into account the individual life situation of the patient. In the context of ICT, the administration of an additional hypoglycaemic agent is not usually considered indicated. In addition to CT, metformin may be administered, if necessary.

Taking into account the available evidence and the written statement procedure, a patient-individual therapy therefore represents the appropriate comparator therapy, taking into account the HbA1c value, previous therapies and complications (e.g. the occurrence of ketoacidosis). As part of the patient-individual therapy, the following escalation therapies are available for children and adolescents aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least one hypoglycaemic agent in addition to diet and exercise: Metformin + human insulin, metformin + liraglutide or an escalation of insulin therapy in the form of conventional insulin therapy (CT, mixed insulin if necessary + metformin) or intensified conventional insulin therapy (ICT).

The continuation of an inadequate therapy (regimen) for the treatment of type 2 diabetes mellitus, if there are still possibilities of therapy escalation, does not correspond to the appropriate comparator therapy.

It is assumed that possible comorbidities or risk factors of type 2 diabetes mellitus (e.g. hypertension, dyslipidaemia, microvascular complications - nephropathy, neuropathy, retinopathy) are treated patient-individual according to the current state of medical knowledge, in particular by antihypertensive agents and/or lipid-lowering agents.

According to the current generally recognised state of medical knowledge, there are neither advantages nor disadvantages for insulin analogues compared to human insulin, but there are no long-term data with advantages regarding hard endpoints for insulin analogues. The benefit assessment also considers evidence from studies in which insulin analogues were used, provided that the results from studies with insulin analogues are transferable to human insulin. The authorisation status of the insulin analogues must be taken into account. Study results should be examined for possible effect modification by the type of insulin used if the studies were conducted with both human insulin and insulin analogues.

However, when comparing costs, the treatment costs for human insulin must be taken into account, as this was determined to be the appropriate comparator therapy.

Insulin glargine is an insulin analogue that was not explicitly named as part of the appropriate comparator therapy, but it is nevertheless accepted as a suitable comparator in view of the current data basis.

Change of the appropriate comparator therapy

Up to now, in the present indication of children and adolescents aged 10 to 17 years with insufficiently controlled type 2 diabetes mellitus, a subdivision was made into insulin-naive and insulin-experienced patients. Within the framework of the written statement procedure, however, it became clear that, in addition to previous therapy with insulin, other decision-making criteria such as the HbA1c value, the occurrence of metabolic crises or the life situation of the children and adolescents are crucial. Even if children and adolescents have already received insulin therapy, there is a patient-individual option to choose therapy escalation with another antidiabetic drug (liraglutide) in order to avoid renewed or further insulin therapy (e.g. in overweight patients). The division of the patient population into insulin-naive and insulin-experienced children and adolescents is thus no longer considered appropriate.

For this reason, it is necessary to adapt the appropriate comparator therapy to the current state of medical knowledge and to refrain from splitting the patient population. Rather, a patient-individual treatment decision is indicated, taking into account the HbA1c value, previous therapies and complications.

In addition, the GLP1 agonist liraglutide has now also become established in medical treatment. As part of the patient-individual therapy, an escalation of therapy to metformin + liraglutide should therefore also be considered in the treatment of children and adolescents with type 2 diabetes mellitus who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least one glycaemic agent in addition to diet and exercise.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

Children and adolescents aged 10 to 17 years with type 2 diabetes mellitus, who have not achieved sufficient glycaemic control with their previous medicinal therapy consisting of at least one hypoglycaemic agent in addition to diet and exercise

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of dulaglutide for the treatment of children and adolescents aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus, no relevant study could be identified in comparison with the appropriate comparator therapy.

The pharmaceutical company therefore additionally presents the study H9X-MC-GBGC/AWARD-PEDS (AWARD-PEDS). 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 regimes) with placebo in patients aged 10 to 17 years with type 2 diabetes mellitus who had inadequate glycaemic control despite diet and exercise, with or without metformin and/or basal insulin.

Patients with a glycated haemoglobin (HbA1c) value of > 6.5% to ≤ 11.0% were enrolled. In newly diagnosed patients who have been treated with diet and exercise alone, the HbA1c value should be > 6.5% to ≤ 9.0%. Medicinal treatment of type 2 diabetes mellitus at the time of enrolment in the study was not an inclusion criterion. Medicinal therapy with metformin and/or basal insulin at the time of randomisation had to have been in place at a stable dose for at least 8 weeks prior to screening, with a daily metformin dose of ≥ 1000 mg.

A total of 154 children and adolescents were randomised in a 1:1:1 ratio to one of the following 3 treatment arms: a) 0.75 mg 1 time weekly dulaglutide; b) 0.75 mg 1 time weekly dulaglutide for 4 weeks with subsequent dose increase to 1.5 mg 1 time weekly - if the previous 0.75 mg dose was well tolerated according to the principal investigator's assessment - or c) placebo. Thus, in both dulaglutide arms of the study, there was a deviation from the requirements in the product information. According to the product information, the initial dose for children and adolescents aged 10 to 17 years is 0.75 mg 1 time per week. If necessary, the dose can be increased after at least 4 weeks to a maximum dose of 1.5 mg once a week. In arm a), however, a dose increase to 1.5 mg 1 time per week was not allowed. In arm b), although the dose was increased to 1.5 mg 1 time per week, 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.

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

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

As a result, 63% of the children and adolescents in the placebo arm initially received only monotherapy with metformin as antidiabetic therapy. Thus, for this group of patients, there was no escalation of the already existing (metformin) therapy at the start of the study.

The continuation of an inadequate therapy for the treatment of type 2 diabetes mellitus does not correspond to the implementation of the appropriate comparator therapy, provided that there are still options of therapy escalation. Since the children and adolescents in the placebo arm had a mean HbA1c value of approx. 8.1% at the start of the study, it can be assumed that for the majority of the patients in the placebo arm, a therapy escalation to lower the HbA1c value would have been indicated and possible (e.g. by adding insulin or liraglutide). Overall, the lack of optimisation of the existing therapy at the time of randomisation in the placebo arm thus leads to the fact that the appropriate comparator therapy is to be regarded as not being implemented.

In summary, the AWAED-PEDS study submitted by the pharmaceutical company is unsuitable for deriving an additional benefit of dulaglutide compared to the appropriate comparator therapy, as the appropriate comparator therapy was not implemented.

Conclusion

In the overall assessment, no conclusions can be made on the additional benefit of dulaglutide compared to the appropriate comparator therapy on the basis of the study presented. An additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient dulaglutide. The therapeutic indication to be assessed here is as follows:
"For the treatment of children and adolescents aged 10 to 17 years with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin is considered unsuitable due to intolerance or contraindications.
- in addition to other medicinal products for the treatment of diabetes."

The G-BA determined a patient-individual therapy as the appropriate comparator therapy, taking into account the HbA1c value, previous therapies and complications, selecting metformin + human insulin, metformin + liraglutide and an escalation of insulin therapy.

For the assessment of the additional benefit of dulaglutide for the treatment of children and adolescents with inadequately controlled type 2 diabetes mellitus, no relevant study could be identified in comparison with the appropriate comparator therapy.

In addition, the pharmaceutical company presents the AWARD-PEDS study, in which dulaglutide was tested against placebo in children and adolescents with type 2 diabetes mellitus who had inadequate glycaemic control.

During the 26-week double-blind treatment phase, the metformin dose at the start of the study should remain stable and the basal insulin dose should not be increased by more than 15%. Thus, in the placebo arm, there was no escalation of the already existing therapy (e.g. by adding insulin or liraglutide) at the start of the study. The continuation of an inadequate therapy for the treatment of type 2 diabetes mellitus does not correspond to the implementation of the appropriate comparator therapy.

In the overall assessment, no conclusions can be made on the additional benefit of dulaglutide compared to the appropriate comparator therapy on the basis of the study presented. An additional benefit is not proven.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainty due to various methodological aspects. Overall, the data represent an overestimation because the pharmaceutical company did not restrict the target population to children and adolescents with insufficiently controlled type 2 diabetes mellitus in accordance with the marketing authorisation.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of

product characteristics, SmPC) for Trulicity (active ingredient: dulaglutide) at the following publicly accessible link (last access: 28 July 2023):

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 September 2023).

Treatment duration and consumption

With regard to consumption, the average annual consumption was determined by indicating the number of tablets or international units. The daily dosages recommended in the product information were used as a basis for calculation and, if necessary, appropriate ranges were formed. The costs of a possibly necessary titration phase have not been shown, since the anti-diabetic therapy is a continuous long-term therapy and the titration is patient-individual.

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

The weekly starting dose of dulaglutide for children and adolescents aged 10 years and over is 0.75 mg and can be increased to 1.5 mg once a week after at least 4 weeks, if needed.

For metformin, starting doses of 500 mg once daily are recommended for children 10 years and older. Dose increases up to 2,000 mg metformin daily are possible according to the product information; the total daily dose is usually divided into 2 - 3 doses.

The recommended dose of dapagliflozin is 10 mg once daily for all patients 10 years and older.

The daily starting dose of liraglutide for all patients 10 years and older is 0.6 mg; after one week, this is increased to 1.2 mg. According to the product information, patients may benefit from a further increase in the dose from 1.2 mg to 1.8 mg. The appropriate dose of liraglutide is injected subcutaneously daily (pre-filled pen).

A variety of different insulin dosing regimens are available for insulin therapy. In addition, according to the insulin dosing scheme used, the amount of insulin and the frequency of application must be individually adjusted according to the patient's physical activity and lifestyle. To ensure comparability of costs, simplified assumptions have been made for the presentation of treatment duration and dosage. In the "Treatment duration" table, the treatment mode for human insulin (NPH insulin or mixed insulin) is shown as "1 - 2 x daily", although the frequency of application may differ for individual patients.

The insulin dosages (I.U.) per patient are calculated based on the dosage requirement in the age group (children and adolescents from the age of 10 years). The consumption is calculated

based on a dosage requirement of 0.7 to 2 I.U./ kg bw / day for children and adolescents in puberty[2,3].

The basal insulin daily requirement is usually 40 - 60 % of the insulin daily requirement, the remaining requirement is covered accordingly by meal-dependent bolus insulin. Three main meals are assumed when calculating bolus insulin consumption. This information was used to calculate the dose of insulin per patient.

For the calculation of the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. For body weight, a range between 37.6 kg for 10-year-olds and 67.0 kg for 17-year-olds is therefore assumed according to the official representative statistics "Microcensus 2017"[4].

Consequently, weight differences between boys and girls as well as the fact that the bodyweight of patients with type 2 diabetes mellitus may be higher than the average values typical of the age are not taken into account for the cost calculation.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Dulaglutide	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed[5]				
Metformin	Continuously, 1-3 x daily	365.0	1	365.0
Dapagliflozin	Continuously, 1 x daily	365.0	1	365.0
Human insulin (NPH-insulin)	Continuously, 1-2 x daily	365.0	1	365.0
Conventional insulin therapy (CT)[6] mixed insulin	Continuously, 1-2 x daily	365.0	1	365.0
Appropriate comparator therapy				

[2] According to the WHO definition, adolescents from 10 to 19 years of age are in puberty. World Health Organisation. Maternal, Newborn, Child and Adolescent Health and Ageing Data portal [online] URL: https://platform.who.int/data/maternal-newborn-child-adolescent-ageing/adolescent-data

[3] Danne T, Phillip M, Buckingham BA, Jarosz-Chobot P, Saboo B, Urakami T, Battelino T, Hanas R, Codner E. ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and adolescents with diabetes. Paediatric Diabetes. 2018 Oct;19 Suppl 27:115-135. doi: 10.1111/pedi.12718.

[4] Federal Statistical Office, Wiesbaden 2018: https://www.gbe-bund.de

[5] For the combination of dulaglutide with a hypoglycaemic agent, metformin, dapagliflozin and human insulin are presented as possible concomitant active ingredients.

[6] The combination with mixed insulin is shown as an example of the combination of dulaglutide with an insulin in the context of escalation of insulin therapy, in this case with conventional insulin therapy.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
A patient-individual therapy, taking into account the HbA1c value, previous therapies and complications with selection of the following active ingredients:				
Metformin	Continuously, 1-3 x daily	365.0	1	365.0
Human insulin (NPH-insulin)	Continuously, 1-2 x daily	365.0	1	365.0
Liraglutide	Continuously, 1 x daily	365.0	1	365.0
Conventional insulin therapy (CT) mixed insulin	Continuously, 1-2 x daily	365.0	1	365.0
Intensified insulin therapy (ICT)				
Human insulin (NPH-insulin)	Continuously, 1-2 x daily	365.0	1	365.0
Human insulin (bolus insulin)	Continuously, 3 x daily	365.0	1	365.0

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Dulaglutide	0.75 mg - 1.5 mg	0.75 mg - 1.5 mg	1 x 0.75 mg - 1 x 1.5 mg	52.1	52.1 x 0.75 mg - 52.1 x 1.5 mg
Concomitant active ingredient of the medicinal product to be assessed[7]					
Metformin	500 mg - 1,000 mg	500 mg - 2,000 mg	1 x 500 mg - 2 x 1,000 mg	365.0	365.0 x 500 mg - 730.0 x 1,000 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365.0 x 10 mg
Human insulin (NPH-insulin)	0.7 I.U. / kg BW – 2 I.U. / kg BW	26.32 I.U. - 134 I.U.	1 x 26.32 I.U. - 1 x 134 I.U.	365.0	9 x 606.8 I.U. - 48 x 910 I.U.
Conventional insulin therapy (CT) Mixed insulin	0.7 I.U. / kg BW – 2 I.U. / kg BW	26.32 I.U. - 134 I.U.	1 x 26.32 I.U. - 1 x 134 I.U.	365.0	9 x 606.8 I.U. - 48 x 910 I.U.
Appropriate comparator therapy					
A patient-individual therapy, taking into account the HbA1c value, previous therapies and complications with selection of the following active ingredients:					
Metformin	500 mg - 1,000 mg	500 mg - 2,000 mg	1 x 500 mg - 2 x 1,000 mg	365.0	365.0 x 500 mg - 730.0 x 1,000 mg
Human insulin (NPH-insulin)	0.7 I.U. / kg BW – 2 I.U. / kg BW	26.32 I.U. - 134 I.U.	1 x 26.32 I.U. - 1 x 134 I.U.	365.0	9 x 606.8 I.U. - 48 x 910 I.U.

[7] For the combination of dulaglutide with a hypoglycaemic agent, metformin, dapagliflozin and human insulin are presented as possible concomitant active ingredients.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Liraglutide[8]	1.2 mg - 1.8 mg	1.2 mg - 1.8 mg	1 x 1.2 mg - 1 x 1.8 mg	365.0	365.0 x 1.2 mg - 365.0 x 1.8 mg
Conventional insulin therapy (CT)[9]					
Mixed insulin	0.7 I.U. / kg BW – 2 I.U. / kg BW	26.32 I.U. - 134 I.U.	1 x 26.32 I.U. - 1 x 134 I.U.	365.0	9,606.8 I.U. - 48,910 I.U.
Intensified insulin therapy (ICT)					
Human insulin (NPH-insulin)	0.28 I.U./kg BW – 1.2 I.U./kg BW	10.53 I.U. - 80.4 I.U.	1 x 10.53 I.U. - 1 x 80.4 I.U.	365.0	3, 842.72 I.U. - 29, 346 I.U.
Human insulin (Bolus insulin)	0.28 I.U./kg BW – 1.2 I.U./kg BW	10.53 I.U. - 80.4 I.U.	1 x 10.53 I.U. - 1 x 80.4 I.U.	365.0	3, 842.72 I.U. - 29, 346 I.U.

[8] According to the product information, each pre-filled pen contains 18 mg liraglutide in 3 ml solution, corresponding to 10 - 15 single doses. Packs of 2, 5 and 10 pre-filled pens are available.

[9] The combination with mixed insulin is shown as an example of the combination of dulaglutide with an insulin in the context of escalation of insulin therapy, in this case with conventional insulin therapy.

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

The fixed reimbursement rate was used as the basis for calculating the treatment costs for the active ingredients metformin, human insulin and mixed insulin.

In the case of conventional insulin therapy, the costs for mixed insulin (i.e. a human insulin preparation in a specific mixing ratio of 30% normal insulin to 70% basal insulin) were used as a basis.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Dulaglutide 0.75 mg	12 SFI	€ 287.75	€ 2.00	€ 26.24	€ 259.51
Dulaglutide 1.5 mg	12 SFI	€ 287.75	€ 2.00	€ 26.24	€ 259.51
If necessary + metformin 500 mg[10]	180 FCT	€ 16.52	€ 2.00	€ 0.41	€ 14.11
If necessary + metformin 1,000 mg	180 FCT	€ 19.11	€ 2.00	€ 0.62	€ 16.49
If necessary + dapagliflozin 10 mg	98 FCT	€ 239.30	€ 2.00	€ 0.00	€ 237.30
If necessary + human insulin (NPH insulin)[10]	3,000 I.U.	€ 89.98	€ 2.00	€ 6.22	€ 81.76
If necessary + conventional insulin therapy (CT) Mixed insulin[10]	3,000 I.U.	€ 89.98	€ 2.00	€ 6.22	€ 81.76
Appropriate comparator therapy					
Metformin 500 mg[10]	180 FCT	€ 16.52	€ 2.00	€ 0.41	€ 14.11
Metformin 1,000 mg[10]	180 FCT	€ 19.11	€ 2.00	€ 0.62	€ 16.49
Human insulin (NPH insulin)[10]	3,000 I.U.	€ 89.98	€ 2.00	€ 6.22	€ 81.76
Liraglutide 18 mg	100 - 150 SD	€ 660.82	€ 2.00	€ 61.65	€ 597.17
Mixed insulin[10]	3,000 I.U.	€ 89.98	€ 2.00	€ 6.22	€ 81.76
Human insulin (bolus insulin) [10]	3,000 I.U.	€ 89.98	€ 2.00	€ 6.22	€ 81.76

[10] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Abbreviations: SFI = solution for injection i.e. pre-filled pen, SD = single doses, I.U. = international units, FCT = film-coated tablets					

LAUER-TAXE® last revised: 1 September 2023

Costs for additionally required SHI services:

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

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

Costs for additionally required SHI services:

Designation of the therapy	Designation	Cost/ pack[11]	Number	Consumption/ year
Concomitant active ingredient of the medicinal product to be assessed				
Human insulin (NPH insulin)	Blood glucose test strips	€ 15.95	1 – 3 x daily	365 – 1,095
	Lancets	€ 4.20	1 – 3 x daily	365 – 1,095
	Disposable needles	€ 19.95	1 – 2 x daily	365 – 730
Conventional insulin therapy (CT, mixed insulin)	Blood glucose test strips	€ 15.95	1 – 3 x daily	365 – 1,095
	Lancets	€ 4.20	1 – 3 x daily	365 – 1,095
	Disposable needles	€ 19.95	1 – 2 x daily	365 – 730
Appropriate comparator therapy				
Liraglutide	Disposable needles	€ 19.95	1 x daily	365

[11] Number of test strips/ pack = 50 pcs.; number of lancets/ pack = 200 pcs.; number of disposable needles/ pack = 100 pcs.; presentation of the lowest-priced pack according to LAUER-TAXE®, last revised: 1 September 2023.

Designation of the therapy	Designation	Cost/ pack[11]	Number	Consumption/ year
Human insulin (NPH insulin)	Blood glucose test strips	€ 15.95	1 – 3 x daily	365 – 1,095
	Lancets	€ 4.20	1 – 3 x daily	365 – 1,095
	Disposable needles	€ 19.95	1 – 2 x daily	365 – 730
Conventional insulin therapy (CT, mixed insulin)	Blood glucose test strips	€ 15.95	1 – 3 x daily	365 – 1,095
	Lancets	€ 4.20	1 – 3 x daily	365 – 1,095
	Disposable needles	€ 19.95	1 – 2 x daily	365 – 730
Intensified insulin therapy (ICT) Human insulin (NPH insulin) Human insulin (bolus insulin)	Blood glucose test strips	€ 15.95	4 – 6 x daily	1,460 – 2,190
	Lancets	€ 4.20	4 – 6 x daily	1,460 – 2,190
	Disposable needles	€ 19.95	4 – 5 x daily	1,460 – 1,825

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designated medicinal product is an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. This therapeutic indication is a treatment for diabetes mellitus according to the specifications in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the specifications in the product information for the designated medicinal products, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive, which serves search purposes and provided with patient-group-related information on the period of validity of the designation.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 11 January 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 31 March 2023, the pharmaceutical company submitted a dossier for the benefit assessment of dulaglutide to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 March 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient dulaglutide.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 June 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 July 2023. The deadline for submitting statements was 24 July 2023.

The oral hearing was held on 8 August 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 12 September 2023, and the proposed resolution was approved.

At its session on 21 September 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 January 2022	Determination of the appropriate comparator therapy
Working group Section 35a	1 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2023	Conduct of the oral hearing
Working group Section 35a	15 August 2023 5 September 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 September 2023	Concluding discussion of the draft resolution
Plenum	21 September 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 21 September 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken