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
Insulin icodec (type 2 diabetes mellitus)

of 20 February 2025

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 all 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient insulin icodec on 1 September 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 29 August 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 December 2024 on the G-BA website (www.g-ba.de), 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 insulin icodec 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 insulin icodec.

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 Insulin icodec (Awiqli) in accordance with the product information

Treatment of diabetes mellitus in adults

Therapeutic indication of the resolution (resolution of 20.02.2025):

Treatment of type 2 diabetes mellitus in adults

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is an indication for an insulin therapy**

Appropriate comparator therapy for insulin icodec:

- Human insulin + metformin

a2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom there is an **indication for an insulin therapy**

Appropriate comparator therapy for insulin icodec:

- human insulin + metformin + empagliflozin, or
- human insulin + metformin + dapagliflozin, or
- human insulin + metformin + liraglutide

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

b1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have **not achieved adequate glycaemic control with their previous insulin regime**, in addition to diet and exercise

Appropriate comparator therapy for insulin icodec:

- Escalation of insulin therapy (conventional therapy (CT) if -necessary + metformin or dulaglutide or intensified insulin therapy (ICT))

b2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have **not achieved adequate glycaemic control with their previous insulin regime**, in addition to diet and exercise

Appropriate comparator therapy for insulin icodec:

- Escalation of insulin therapy: conventional therapy (CT) or intensified insulin therapy (ICT), in each case in combination with metformin and empagliflozin or dapagliflozin or liraglutide

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 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. The following active ingredients or product classes are approved for the treatment of adults with type 2 diabetes mellitus: Alpha-glucosidase inhibitors, DPP-4 inhibitors (gliptins), glinides, GLP-1 receptor agonists (glutides/ incretin mimetics), metformin, SGLT-2 inhibitors (gliflozins), sulphonylureas and insulin (human insulin, insulin analogues).

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

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

Resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication type 2 diabetes mellitus in adults are:

- linagliptin (resolution of 21 February 2013; resolution of 16 May 2013),
- lixisenatide (resolution of 5 September 2013),
- saxagliptin/ metformin (resolution of 1 October 2013; resolution of 15 December 2016; resolution of 1 February 2018),
- vildagliptin (resolution of 1 October 2013; resolution of 21 May 2015),
- vildagliptin/ metformin (resolution of 1 October 2013),
- canagliflozin (resolution of 4 September 2014),
- insulin degludec (resolution of 16 October 2014; resolution of 20 August 2015; resolution of 16 May 2019),
- canagliflozin/ metformin (resolution of 5 February 2015),
- albiglutide (resolution of 19 March 2015),
- insulin degludec/ liraglutide (resolution of 15 October 2015; resolution of 4 February 2016),
- empagliflozin (resolution of 1 September 2016),
- empagliflozin/ metformin (resolution of 1 September 2016),
- saxagliptin (resolution of 15 December 2016),
- sitagliptin (resolution of 15 December 2016; resolution of 22 March 2019),

- sitagliptin/ metformin (resolution of 15 December 2016),
- insulin glargine/ lixisenatide (resolution of 16 August 2018; resolution of 15 October 2020),
- ertugliflozin/ sitagliptin (resolution of 1 November 2018),
- empagliflozin/ linagliptin (resolution of 22 November 2019),
- dapagliflozin (resolution of 19 December 2019),
- dapagliflozin/ metformin (resolution of 19 December 2019),
- dulaglutide (resolution of 16 July 2020),
- semaglutide (resolution of 15 April 2021),
- ertugliflozin (resolution of 19 May 2022),
- tirzepatide (resolution of 2 May 2024).

Furthermore, there are prescription restrictions for the fast-acting insulin analogues insulin aspart, insulin glulisine and insulin lispro as well as for the long-acting insulin analogues insulin glargine and insulin determir in the present indication in accordance with Annex III Nos. 33 and 33a of the Pharmaceuticals Directive.

Accordingly, the fast-acting insulin analogues insulin aspart, insulin glulisine and insulin lispro cannot be prescribed as long as they are associated with additional costs compared to fast-acting human insulin. The pursued therapeutic goal can be achieved just as effectively with human insulin, but at a lower cost. The actual costs incurred by the responsible statutory health insurance are decisive for determining the additional costs. This does not apply to patients

- allergic to the active ingredient human insulin,
- in whom a stable, adequate metabolic situation cannot be achieved with human insulin despite intensification of therapy; nevertheless, this has been proven to be possible with fast-acting insulin analogues,
- for whom therapy with fast-acting insulin analogues is more economical in individual cases due to disproportionately high doses of human insulin.

Similarly, the long-acting insulin analogues insulin glargine and insulin determir cannot be prescribed as long as they are associated with additional costs compared to intermediate-acting human insulin, taking into account the dosages required to achieve the therapeutic goal. The pursued therapeutic goal can be achieved just as effectively with human insulin, but at a lower cost. The actual costs incurred by the responsible statutory health insurance are decisive for determining the additional costs.
These regulations do not apply to

- treatment with insulin glargine in patients in whom a high risk of severe hypoglycaemias persists in individual cases as part of intensified insulin therapy, even after individual review of the therapeutic goal and individual adjustment of the extent of blood glucose reduction,
- patients with allergies to intermediate-acting human insulins.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic 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.

Based on the results of cardiovascular Outcome studies and the recommendations of the guideline[2], which indicate that the most robust data were shown in diabetics with existing cardiovascular disease, a distinction is made between patients **with and without manifest cardiovascular disease** for the determination of the appropriate comparator therapy.

In the presence of manifest cardiovascular disease, positive effects on cardiovascular endpoints were proven for the SGLT-2 inhibitors empagliflozin and dapagliflozin as combination therapy with other anti-diabetics.
The corresponding EMPA-REG-Outcome and DECLARE-TIMI 58 studies were assessed as part of the early benefit assessment and an additional benefit of both empagliflozin and dapagliflozin was identified. For the GLP-1-RA liraglutide as a combination therapy with other anti-diabetics, advantages in the reduction of cardiovascular events were also demonstrated on the basis of the LEADER study. For this reason, the active ingredients empagliflozin, dapagliflozin and liraglutide are named as part of the appropriate comparator therapy for the sub-populations with manifest cardiovascular disease (**patient groups a2 and b2).**

In the considered therapeutic indication of insulin icodec for the treatment of type 2 diabetes mellitus, it is assumed that insulin therapy is indicated for the target population.

The guideline[2] recommends insulin therapy in the following scenarios:

- if the individual therapeutic goal is not achieved despite exhaustion of non-medical measures and medicinal therapy (combination of oral anti-diabetics with/without GLP-1-RA to be administered SC),
- in the case of metabolic derangements, e.g. on initial diagnosis (unclear diagnostic situation, type 1 diabetes cannot be ruled out with certainty),
- when administering diabetogenic medication (e.g. glucocorticoids), in the case of severe infections, trauma or major operations (possibly only temporarily),
- in the case of severely impaired renal function (depending on the individual therapeutic goal).

Overall, according to the guideline, permanent insulin therapy is only indicated when other medicinal options with non-insulin anti-diabetics have already been exhausted.

The benefit of human insulin has been proven by the reduction of diabetes-related microvascular complications[3]. The guideline group recommends basal supported oral therapy (BOT) when starting insulin therapy in insulin-naive patients. A combination therapy consisting of basal insulin and metformin is recommended for subjects without manifest cardiovascular disease **(patient group a1)**. In the presence of

[2] German National Disease Management Guideline (NDMG): Type 2 diabetes, long version – Version 3.0 https://register.awmf.org/assets/guidelines/nvl-001l_S3_Typ-2-Diabetes_2024-12.pdf [published on 15.05.2023]

[3] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131):837-853

manifest cardiovascular disease, the BOT includes the combination of basal insulin with metformin and empagliflozin or dapagliflozin or liraglutide **(patient group a2).**

According to the guideline[2], escalation of insulin therapy is indicated if patients do not achieve their individual therapeutic goal with a combination therapy consisting of basal insulin and other non-insulin anti-diabetics (BOT) **(patient group b)**. For this purpose, either conventional insulin therapy (CT) or intensified conventional insulin therapy (ICT) should be carried out. CT involves the combined administration of basal insulin and short-acting insulin (mixed insulin). In ICT, the insulin requirement is divided into long-acting basal insulin and short-acting insulin at mealtimes and determined individually (basal-bolus principle). The choice of CT or ICT here is based on the patient-individual living conditions and lifestyle. Due to its complexity and greater effort, the insulin regimen of ICT represents the final escalation stage of insulin therapy. Accordingly, no further intensification of therapy can be carried out for patients who do not reach their individual target values under ICT. For these subjects, it should be checked whether a dose adjustment or a change of insulin is indicated. It is also recommended that patients be trained more closely in the use of ICT.

A more intensive insulin therapy in the form of a CT, if necessary + metformin or dulaglutide, or an ICT is determined to be the appropriate comparator therapy for the patient population without manifest cardiovascular disease who have not achieved adequate glycaemic control with their current insulin therapy, in particular a BOT. On the basis of the AWARD 4 and AWARD 7 studies, an additional benefit was identified for the use of dulaglutide in insulin-dependent patients without manifest cardiovascular disease **(patient group b1)**.

In the presence of manifest cardiovascular disease, the guideline group recommends continuing the initial therapy consisting of metformin and empagliflozin, dapagliflozin or liraglutide as part of the escalation of insulin therapy, provided that this therapy is well tolerated in combination with insulin. Consequently, the appropriate comparator therapy in this therapy level is CT or ICT, in each case in combination with metformin and empagliflozin or dapagliflozin or liraglutide **(patient group b2)**.

Patients receiving insulin should be regularly checked to see whether the indication for insulin therapy still exists or whether de-escalation of insulin therapy is possible and indicated.

According to the current generally recognised state of medical knowledge, insulin analogues have neither advantages nor disadvantages compared to human insulin. However, there are no long-term data with advantages with regard to hard endpoints for insulin analogues. Studies with insulin analogues as comparator are considered for the early benefit assessment. The regulations in Annex III of the Pharmaceuticals Directive must be observed.

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

It is assumed that comorbidities in adults with type 2 diabetes mellitus (such as hypertension, dyslipoproteinaemias, CHD, renal disease, etc.) and in particular concomitant manifest cardiovascular disease are subject to patient-individual treatment of the respective comorbidities, in particular with anti-hypertensive drugs, anticoagulants and/or lipid-lowering agents, in accordance with the recognised state of medical knowledge.

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 insulin icodec is assessed as follows:

a1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom **there is an indication for an insulin therapy**.

An additional benefit is not proven.

a2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current medicinal therapy consisting of at least two hypoglycaemic agents**, in addition to diet and exercise, and for whom there is an **indication for an insulin therapy**.

An additional benefit is not proven.

b1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current insulin regimen**, in addition to diet and exercise

An additional benefit is not proven.

b2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current insulin regimen**, in addition to diet and exercise

An additional benefit is not proven.

Justification:

Patient population a1)

Data from a sub-population of the ONWARDS 1 study were presented for the assessment of the additional benefit of insulin icodec for the treatment of insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current therapy consisting of at least two hypoglycaemic agents and for whom insulin therapy is indicated for the first time.

ONWARDS 1 study

ONWARDS 1 is an open-label, randomised, active-controlled study with a treatment duration of 78 weeks. In the study, the administration of insulin icodec was compared with insulin glargine, in each case in combination with non-insulin anti-diabetics. The primary endpoint was the change in the HbA1c value. Other endpoints in the morbidity category and adverse

events were also collected. Health-related quality of life was not collected in the ONWARDS 1 study.

Population of the ONWARDS 1 study and relevant sub-population for the benefit assessment

Insulin-naive adults who had an HbA1c value in the range ≥ 7.0% to ≤ 11.0% and a BMI ≤ 40 kg/m^2 at the start of the study were enrolled in the ONWARDS 1 study. According to the exclusion criteria, patients whose glycaemic control could be influenced by any change in their lifestyle were excluded.

The continuation of stable prior therapy, consisting of metformin alone or combinations of metformin and DPP-4 inhibitors, SGLT-2 inhibitors, glitazones, alpha-glucosidase inhibitors or oral or injectable GLP1-RA, was permitted as concomitant therapy during the treatment phase. According to the inclusion criteria, the previous therapy had to have been administered at a stable dose for at least 90 days before the start of the study. Patients who had received sulphonylureas or glinides as prior therapy could be enrolled, but had to discontinue them prior to randomisation.

A total of 984 insulin-naive adults were allocated in a 1:1 ratio to the insulin icodec or insulin glargine treatment arms *(in each case, 492 subjects per treatment arm).* The sub-population of patients who were treated in the study with insulin icodec or insulin glargine, in each case in combination with metformin is relevant for the early benefit assessment. In addition, the relevant sub-population had to have been treated with a prior therapy consisting of at least two hypoglycaemic agents. For the relevant sub-population, this resulted in 37 subjects in the intervention arm with insulin icodec and 28 subjects in the comparator arm with insulin glargine.

Uncertainties regarding the target values and the indication for insulin therapy

Insulin icodec was administered in the intervention arm according to the requirements in the product information. According to the study protocol, the individual dose of insulin icodec should be adjusted every week to every two weeks. This only partially corresponds to the requirements in the product information, which stipulates a weekly dose adjustment of insulin icodec. In the comparator arm, the administration of insulin glargine was in accordance with the requirements in the product information.

In both treatment arms, a fasting blood glucose target value in the range of 80 to 130 mg/dl was specified. Accordingly, the individual dose of insulin should be adjusted according to a defined titration algorithm. In the study, the target value-based treatment only applied to fasting blood glucose for the purpose of insulin titration. In contrast, no patient-individual target values for the HbA1c value were specified in the study, although this is explicitly recommended in the German National Disease Management Guideline[2]. According to the guideline, individualised HbA1c therapeutic goals should be agreed according to the respective needs of the patients. Various factors such as age, physical condition, comorbidities, duration of diabetes, risk of hypoglycaemia, etc. should be taken into account. Depending on these personal factors, adults with type 2 diabetes mellitus benefit from different target values. The individualisation of the HbA1c target value is of great significance in diabetes treatment. The procedure in the study therefore does not comply with the guideline recommendation with regard to the lack of agreement on patient-individual HbA1c target values.

In addition, the ONWARDS 1 study did not adequately ensure that first-time treatment with insulin was clearly indicated for all insulin-naive patients enrolled. According to the guideline recommendation, the indication for insulin treatment must be carefully checked before starting insulin therapy. As a result, the indication for long-term insulin therapy is only given when other medicinal options with oral or subcutaneous anti-diabetics (e.g. GLP-1-RA) have already been exhausted. Therefore, prior to first-time use of insulin therapy, treatment with oral dual combination therapy or, if this is insufficient, intensification with an additional or alternative anti-diabetic including GLP-1-RA (other than insulin) may be considered. However, it is not clear from the ONWARDS 1 study documents that the patients enrolled in the study met the requirements specified in the guideline for the indication of insulin therapy. It is therefore not possible to conclusively assess whether treatment with insulin was actually indicated for the study population, or whether an intensification with a combination therapy of metformin and other non-insulin anti-diabetics in accordance with the algorithm for medicinal therapy according to the guideline would have been more suitable instead.

Conclusion of the ONWARDS 1 study

In the overall assessment, the ONWARDS 1 study is unsuitable for the present assessment. On the one hand, it cannot be assumed with certainty that all patients in the study actually had an indication for insulin therapy. On the other, the guideline recommendation on setting patient-individual target values for the HbA1c value was not followed in the study. Due to these limitations, no conclusions on the additional benefit of insulin icodec in the treatment of insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease can be drawn on the basis of the study.

An additional benefit is therefore not proven.

Patient population a2)

No data were presented for the assessment of the additional benefit of insulin icodec for the treatment of insulin-naive adults with type 2 diabetes mellitus and manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current therapy consisting of at least two hypoglycaemic agents and for whom insulin therapy is indicated for the first time.

An additional benefit is therefore not proven.

Patient population b1)

Data from a sub-population of the ONWARDS 4 study were provided to assess the additional benefit of insulin icodec for the treatment of adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current insulin regimen.

ONWARDS 4 study

The open-label, randomised, active-controlled ONWARDS 4 study investigates the comparison of insulin icodec versus insulin glargine, in each case in combination with insulin aspart, in insulin-experienced adults. The comparative treatment phase of the study lasted 26 weeks. The primary endpoint was the change in the HbA1c value. Other endpoints of morbidity and adverse events were also collected. Health-related quality of life was not collected in the ONWARDS 4 study.

Population of the ONWARDS 4 study and relevant sub-population for the benefit assessment

Insulin-experienced adults who had an HbA1c value in the range ≥ 7.0% to ≤ 10.0% and a BMI ≤ 40 kg/m^2 at the start of the study were enrolled in the ONWARDS 4 study. According to the exclusion criteria, patients who had been diagnosed with a hypoglycaemia perception disorder or had previously experienced recurrent severe hypoglycaemias or diabetic ketoacidosis were excluded. Another exclusion criterion was defined as a probable change in lifestyle with an influence on glycaemic control.

In addition to the test intervention with insulin icodec or insulin glargine, in each case combined with the bolus insulin aspart, the non-insulin anti-diabetics from the previous therapy, which had been administered at a stable dose for at least 90 days before the start of the study, could be continued as concomitant therapy in the study. The non-insulin anti-diabetic previous therapy included metformin, sulphonylureas, glinides, DPP-4 inhibitors, glitazones, SGLT-2 inhibitors, alpha-glucosidase inhibitors and oral or injectable GLP1-RA, whereby sulphonylureas and glinides had to be discontinued before the start of the study. In addition, patients had to have received insulin therapy consisting of basal insulin and a bolus insulin analogue for at least 90 days prior to enrolment in the study.

A total of 582 patients were allocated in a 1:1 ratio to the insulin icodec or insulin glargine treatment arms *(in each case, 291 subjects per treatment arm).* The sub-population of patients who were treated in the study solely with insulin icodec or insulin glargine and the bolus insulin aspart is relevant for the early benefit assessment. Accordingly, the sub-population only included those adults who only received ICT without non-insulin anti-diabetics at the time of enrolment in the study or who had been pretreated with sulphonylureas and/or glinides, as these had to be discontinued before receiving the study medication. For the relevant sub-

population, this resulted in 57 subjects in the intervention arm and 52 subjects in the comparator arm.

Uncertainties of the ONWARDS 4 study

Insulin icodec was administered largely in accordance to the requirements in the product information. All patients received a 50% loading dose of the initial dose of insulin icodec, which is only recommended according to the product information if the aim is to achieve glycaemic control more quickly. However, it is unclear whether this was necessary for all subjects. In the comparator arm, the administration of insulin glargine was in accordance with the requirements in the product information. In the study, all patients received insulin aspart as bolus insulin. However, the insulin aspart dose had to be kept stable for the first eight weeks, although this does not correspond to the requirements in the product information for insulin icodec and insulin aspart. This is because the dose and timing of the concomitant administration of bolus insulin preparations have to be adjusted for the switch to insulin icodec according to the product information. The product information for insulin aspart also recommends adjusting the insulin dose, especially at the start of treatment. In the study, adjustments could nevertheless only be made in the first eight weeks for safety reasons.

With regard to the blood glucose target values, the ONWARDS 4 study has a study design similar to the ONWARDS 1 study. There was also a fixed range for fasting blood glucose between 80 and 130 mg/dl. The dose of basal and bolus insulin *(only from week 8 for bolus insulin)* was adjusted using a predetermined titration algorithm. Patient-individual target values for HbA1c were not defined in this study either. Consequently, the guideline recommendations in the ONWARDS 4 study have not been implemented in this respect either. In view of the great significance of patient-individual therapeutic goals for the successful treatment of type 2 diabetes, the study also has methodological limitations in this respect.

The patients examined in the ONWARDS 4 study were therefore receiving ICT even before enrolment in the study. As ICT is already the final escalation stage of insulin therapy, it must be assumed that other less complex insulin regimens had already been exhausted for the study population. Against this background, the only option left for further optimisation of the therapy was to change the insulin administered and adjust the insulin dose. As almost 70% of the total population in the comparator arm had received insulin glargine and 50% insulin aspart even before randomisation, the insulins used in the previous therapy were continued in these subjects during the study. However, there is no information on the insulins used before the start of the study for the relevant sub-population presented. It is therefore not possible to estimate how many subjects in the comparator arm had a change of insulin. In addition, it is not possible to estimate the extent to which the patients in the comparator arm experienced optimisation in terms of insulin dose adjustment. One reason for this is the requirement that bolus insulin therapy had to be stable in the first eight weeks, and another is that no data were available to provide information on the percentage of adults in the sub-population with dose adjustments. Overall, the correct implementation of the appropriate comparator therapy cannot be conclusively assessed.

Conclusion of the ONWARDS 4 study

In the overall assessment, the ONWARDS 4 study is unsuitable for the present assessment due to methodological limitations. On the one hand, there were deviations from the recommendations of the guideline and the product information. On the other, the correct implementation of the appropriate comparator therapy cannot be conclusively assessed. Overall, no conclusions on the additional benefit of insulin icodec in the treatment of insulin-

experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease can therefore be drawn on the basis of the study.

An additional benefit is therefore not proven.

Patient population b2)

No data were provided to assess the additional benefit of insulin icodec for the treatment of adults with type 2 diabetes mellitus and manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current insulin regimen.

An additional benefit is therefore not proven.

2.1.4 Summary of the assessment

This is the early benefit assessment of the new medicinal product Awiqli with the active ingredient insulin icodec for the treatment of adults with type 2 diabetes mellitus.

A distinction was made between four patient populations in the therapeutic indication to be considered.

Patient group a1)

For insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved sufficient glycaemic control with their current medicinal therapy consisting of at least two blood glucose-lowering drugs in addition to diet and exercise, and for whom there is an indication for insulin therapy, the following was determined by the G-BA as the appropriate comparator therapy:

- Human insulin + metformin.

A sub-population of the ONWARDS 1 study was presented. This sub-population comprises insulin-naive adults who were treated with insulin icodec or insulin glargine, in each case, in combination with metformin in the study.

Overall, it cannot be assumed with certainty that all subjects actually had an indication for insulin therapy. In addition, the guideline recommendation on setting patient-individual target values was not followed. Due to these limitations, no statements on the additional benefit of insulin icodec can be derived on the basis of the ONWARDS 1 study. An additional benefit is therefore not proven.

Patient group a2)

For insulin-naive adults with type 2 diabetes mellitus and manifest cardiovascular disease who have not achieved sufficient glycaemic control with their current medicinal therapy consisting of at least two blood glucose-lowering drugs in addition to diet and exercise, and for whom there is an indication for insulin therapy, the following was determined by the G-BA as the appropriate comparator therapy:

- human insulin + metformin + empagliflozin, or
- human insulin + metformin + dapagliflozin, or
- human insulin + metformin + liraglutide.

No data were presented versus the appropriate comparator therapy. An additional benefit is therefore not proven.

Patient group b1)

For insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current insulin regimen, in addition to diet and exercise, the following was determined by the G-BA to be an appropriate comparator therapy:

- escalation of insulin therapy (conventional therapy (CT) if necessary + metformin or dulaglutide or intensified insulin therapy (ICT)).

A sub-population of the ONWARDS 4 study was presented. This sub-population comprises insulin-experienced adults who were treated in the study exclusively with insulin icodec or insulin glargine and the bolus insulin, insulin aspart.

The ONWARDS 4 study is unsuitable due to methodological limitations. On the one hand, there were deviations from the recommendations of the guideline and the product information. On the other, the correct implementation of the appropriate comparator therapy cannot be conclusively assessed. Overall, no conclusions on the additional benefit of insulin icodec in the treatment of insulin-experienced adults can therefore be drawn on the basis of the study. An additional benefit is therefore not proven.

Patient group b2)

For insulin-experienced adults with type 2 diabetes mellitus and manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current insulin regimen, in addition to diet and exercise, the following was determined by the G-BA to be an appropriate comparator therapy:

- Escalation of insulin therapy: conventional therapy (CT) or intensified insulin therapy (ICT), in each case in combination with metformin and empagliflozin or dapagliflozin or liraglutide.

No data were presented versus the appropriate comparator therapy. An additional benefit is therefore 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 resolution is based on the patient numbers stated in the dossier of the pharmaceutical company, based on the information in the previous resolution in this therapeutic indication.

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 Awiqli (active ingredient: insulin icodec) at the following publicly accessible link (last access: 6 January 2025):

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

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2025).

With regard to consumption, the average annual consumption was determined by indicating the number of tablets or individual doses. 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.

According to the product information, insulin icodec is a basal insulin that is administered once a week. Insulin icodec can be used as monotherapy as well as in combination with oral anti-diabetics, GLP-1 receptor agonists and bolus insulin.

For metformin, starting doses of 500 mg or 850 mg two to three times daily are recommended, but dose increases up to 3,000 mg metformin daily are possible; the total daily dose is usually divided into 2 - 3 doses. Therefore, an potency of 1,000 mg metformin/tablet is used as the basis for the cost representation.

The starting dose of liraglutide 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).

For empagliflozin, a starting dose of 10 mg once daily is recommended as combination therapy with other hypoglycaemic agents, including insulin. If metabolic control is inadequate, the dose may be increased to 25 mg once daily. Therefore, both potencies are taken into account for the cost representation.

The recommended dose of dapagliflozin is 10 mg once daily.

For dulaglutide, as part of combination therapy with other medicines, a dose of 1.5 mg once weekly is recommended, which can be increased to a maximum dose of 4.5 mg once weekly.

The potency of the insulin analogue insulin icodec is expressed in units (U.). One unit of insulin icodec corresponds to one international unit (I.U.) Human insulin.

A variety of different insulin dosage regimens are available for insulin therapy. In addition, according to the insulin dosage regimen 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. According to the product information, the average insulin requirement is often 0.5 - 1.0 I.U. per kg body weight (kg BW) per day. 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. Therefore, an average bodyweight of 77.7 kg is assumed for the bodyweight according to the official representative statistics "Microcensus 2021"[4].

Consequently, weight differences between women and men and the increased BMI of the patient population are not taken into account in the cost calculation.

Treatment period:

a1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control with their current medicinal **therapy consisting of at least two hypoglycaemic agents,** in addition to diet and exercise, and for whom there is an **indication for an insulin therapy.**

Designation of the therapy	Treatment mode	Number of treatments/ subject /year	Treatment duration/ treatment (days)	Treatment days/ subject/ year
Medicinal product to be assessed				
Insulin icodec	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed				
Metformin	Continuously, 2 - 3 x daily	365.0	1	365.0
Appropriate comparator therapy				
Metformin	Continuously, 2 - 3 x daily	365.0	1	365.0
Human insulin (NPH insulin)	Continuously, 1 – 2 x daily	365.0	1	365.0

[4] Federal health reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

a2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control with their current medicinal **therapy consisting of at least two hypoglycaemic agents,** in addition to diet and exercise, and for whom there is an **indication for an insulin therapy.**

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ subject/ year
Medicinal product to be assessed				
Insulin icodec	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed				
Metformin	Continuously, 2 - 3 x daily	365.0	1	365.0
Empagliflozin	Continuously, 1 x daily	365.0	1	365.0
Dapagliflozin	Continuously, 1 x daily	365.0	1	365.0
Liraglutide	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Metformin	Continuously, 2 - 3 x daily	365.0	1	365.0
Empagliflozin	Continuously, 1 x daily	365.0	1	365.0
Dapagliflozin	Continuously, 1 x daily	365.0	1	365.0
Liraglutide	Continuously, 1 x daily	365.0	1	365.0
Human insulin (NPH insulin)	Continuously, 1 – 2 x daily	365.0	1	365.0

b1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current insulin regimen**, in addition to diet and exercise

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ subject/ year
Medicinal product to be assessed				
Insulin icodec	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed				
Metformin	Continuously, 2 - 3 x daily	365.0	1	365.0
Human insulin (bolus insulin)	Continuously, 3 x daily	365.0	1	365.0
Appropriate comparator therapy				
Metformin	Continuously, 2 - 3 x daily	365.0	1	365.0
Dulaglutide	Continuously, 1 x every 7 days	52.1	1	52.1
Conventional insulin therapy (CT) Mixed insulin	Continuously, 1 - 2 x daily	365.0	1	365.0
Intensified insulin therapy (ICT) Human insulin (NPH insulin) Human insulin (bolus insulin)	 Continuously, 1 - 2 x daily Continuously, 3 x daily	 365.0 365.0	 1 1	 365.0 365.0

b2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have **not achieved adequate glycaemic control with their current insulin regimen**, in addition to diet and exercise

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ subject/ year
Medicinal product to be assessed				
Insulin icodec	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed				
Metformin	Continuously, 2 - 3 x daily	365.0	1	365.0
Human insulin (bolus insulin)	Continuously, 3 x daily	365.0	1	365.0
Appropriate comparator therapy				
Metformin	Continuously, 2 - 3 x daily	365.0	1	365.0
Empagliflozin	Continuously, 1 x daily	365.0	1	365.0
Dapagliflozin	Continuously, 1 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) Human insulin (bolus insulin)	Continuously, 1 - 2 x daily Continuously, 3 x daily	365.0 365.0	1 1	365.0 365.0

Consumption:

a1) **Insulin-naive** adults with type 2 diabetes mellitus **without manifest cardiovascular** disease, who have not achieved adequate glycaemic control with their current medicinal **therapy consisting of at least two hypoglycaemic agents,** in addition to diet and exercise, and for whom there is an **indication for an insulin therapy.**

Designation of the therapy	Dosage/ application	Dose/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Insulin icodec	3.5 U. - 7 U./ kg BW	271.95 U. - 543.9 U.	1 x 271.95 U. - 1 x 543.9 U.	52.1	14,168.60 U. - 28,337.19 U.
Concomitant active ingredient of the medicinal product to be assessed					
Metformin	500 mg - 1,000 mg	1000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0	365 x 1,000 mg - 1,095 x 1,000 mg
Appropriate comparator therapy					
Metformin	500 mg - 1,000 mg	1000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0	365 x 1,000 mg - 1,095 x 1,000 mg
Human insulin (NPH insulin)	0.5 I.U. - 1.0 I.U. / kg BW	38.85 I.U. - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365.0	14,180.25 I.U. - 28,360.5 I.U.

a2) **Insulin-naive** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have not achieved adequate glycaemic control with their current medicinal **therapy consisting of at least two hypoglycaemic agents,** in addition to diet and exercise, and for whom there is an **indication for an insulin therapy.**

Designation of the therapy	Dosage/ application	Dose/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Insulin icodec	3.5 U. - 7 U./ kg BW	271.95 U. - 543.9 U.	1 x 271.95 U. - 1 x 543.9 U.	52.1	14,168.60 U. - 28,337.19 U.
Concomitant active ingredient of the medicinal product to be assessed					
Metformin	500 mg - 1,000 mg	1000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0	365 x 1,000 mg - 1,095 x 1,000 mg

Designation of the therapy	Dosage/ application	Dose/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365.0	365 x 10 mg - 365 x 25 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Liraglutide	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 x 1.2 mg - 365 x 1.8 mg
Appropriate comparator therapy					
Metformin	500 mg - 1,000 mg	1000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0	365 x 1,000 mg - 1,095 x 1,000 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365.0	365 x 10 mg - 365 x 25 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Liraglutide	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 x 1.2 mg - 365 x 1.8 mg
Human insulin (NPH insulin)	0.5 I.U. - 1.0 I.U. / kg BW	38.85 I.U. - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365.0	14,180.25 I.U. - 28,360.5 I.U.

b1) **Insulin-experienced** adults with type 2 diabetes mellitus **without manifest cardiovascular disease**, who have not achieved adequate glycaemic control **with their current insulin regimen**, in addition to diet and exercise

Designation of the therapy	Dosage/ application	Dose/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Insulin icodec	1.4 U. - 4.2 U. / kg BW[5]	108.8 U. - 326.3 U.	1 x 108.8 U. - 1 x 326.3 U.	52.1	5,667.4 U. - 17,002.3 U.
Concomitant active ingredient of the medicinal product to be assessed					
Metformin	500 mg - 1,000 mg	1000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0	365 x 1,000 mg - 1,095 x 1,000 mg
Human insulin (bolus insulin)	0.2 I.U. -	15.54 I.U. - 46.62 I.U.	1 x 15.54 I.U. - 1 x 46.62 I.U.	365.0	5,672.1 I.U. - 17,016.3 I.U.

[5] 40% to 60% share of insulin icodec in combination with bolus insulin

Designation of the therapy	Dosage/ application	Dose/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
	0.6 I.U. / kg BW				
Appropriate comparator therapy					
Metformin	500 mg - 1,000 mg	1000 mg - 3,000 mg	1 x 1000 mg 3 x 1,000 mg	365.0	365 x 1,000 mg - 1,095 x 1,000 mg
Dulaglutide	1.5 mg - 4.5 mg	1.5 mg - 4.5 mg	1 x 1.5 mg - 1 x 4.5 mg	52.1	52.1 x 1.5 mg - 52.1 x 4.5 mg
Conventional insulin therapy (CT) Mixed insulin	0.5 I.U. - 1.0 I.U. / kg BW	38.85 I.U. - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365.0	14,180.25 I.U. - 28,360.5 I.U.
Intensified insulin therapy (ICT) Human insulin (NPH insulin) + Human insulin (bolus insulin)	0.2 I.U. - 0.6 I.U./kg BW 0.2 I.U. - 0.6 I.U./kg BW	15.54 I.U. - 46.62 I.U. 15.54 I.U. - 46.62 I.U.	1 x 15.54 I.U. - 1 x 46.62 I.U. 1 x 15.54 I.U. - 1 x 46.62 I.U.	365.0 365.0	5,672.1 I.U. - 17,016.3 I.U. 5,672.1 I.U. - 17,016.3 I.U.

b2) **Insulin-experienced** adults with type 2 diabetes mellitus **with manifest cardiovascular disease**, who have **not achieved adequate glycaemic control with their current insulin regimen**, in addition to diet and exercise

Designation of the therapy	Dosage/ application	Dose/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Insulin icodec	1.4 U. - 4.2 U./ kg BW[5]	108.8 U. - 326.3 U.	1 x 108.8 U. - 1 x 326.3 U.	52.1	5,667.4 U. - 17,002.3 U.
Concomitant active ingredient of the medicinal product to be assessed					
Metformin	500 mg - 1,000 mg	1000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0	365 x 1,000 mg - 1,095 x 1,000 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365.0	365 x 10 mg - 365 x 25 mg

Designation of the therapy	Dosage/ application	Dose/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Liraglutide	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 x 1.2 mg - 365 x 1.8 mg
Human insulin (bolus insulin)	0.2 I.U. - 0.6 I.U./kg BW	15.54 I.U. - 46.62 I.U.	1 x 15.54 I.U. - 1 x 46.62 I.U.	365.0	5,672.1 I.U. - 17,016.3 I.U.
Appropriate comparator therapy					
Metformin	500 mg - 1,000 mg	1000 mg - 3,000 mg	1 x 1,000 mg - 3 x 1,000 mg	365.0	365 x 1,000 mg - 1,095 x 1,000 mg
Empagliflozin	10 mg - 25 mg	10 mg - 25 mg	1 x 10 mg - 1 x 25 mg	365.0	365 x 10 mg - 365 x 25 mg
Dapagliflozin	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Liraglutide	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 x 1.2 mg - 365 x 1.8 mg
Conventional insulin therapy (CT) mixed insulin	0.5 I.U. - 1.0 I.U./kg BW	38.85 I.U. - 77.7 I.U.	1 x 38.85 I.U. - 1 x 77.7 I.U.	365.0	14,180.25 I.U. - 28,360.5 I.U.
Intensified insulin therapy (ICT) Human insulin (NPH insulin) + Human insulin (bolus insulin)	0.2 I.U. - 0.6 I.U./kg BW 0.2 I.U. - 0.6 I.U./kg BW	15.54 I.U. - 46.62 I.U. 15.54 I.U. - 46.62 I.U.	1 x 15.54 I.U. - 1 x 46.62 I.U. 1 x 15.54 I.U. - 1 x 46.62 I.U.	365.0 365.0	5,672.1 I.U. - 17,016.3 I.U. 5,672.1 I.U. - 17,016.3 I.U.

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 Sections 130 and 130 a 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

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

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:

Patient populations a1), a2), b1), b2)

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					
Insulin icodec 700 U./ml	4,200 U.	€ 260.80	€ 1.77	€ 13.81	€ 245.22
Concomitant active ingredient of the medicinal product to be assessed					
Metformin 1,000 mg[6]	180 FCT	€ 19.11	€ 1.77	€ 0.62	€ 16.72
Dapagliflozin 10 mg	98 FCT	€ 237.65	€ 1.77	€ 0.00	€ 235.88
Empagliflozin 10 mg	100 FCT	€ 238.35	€ 1.77	€ 12.57	€ 224.01
Empagliflozin 25 mg	100 FCT	€ 191.05	€ 1.77	€ 9.95	€ 179.33
Human insulin (bolus insulin) 100 I.U./ml[6]	3,000 I.U.	€ 89.98	€ 1.77	€ 6.22	€ 81.99
Liraglutide 18 mg	100 - 150 SD	€ 699.15	€ 1.77	€ 38.08	€ 659.30
Appropriate comparator therapy					
Metformin 1,000 mg[6]	180 FCT	€ 19.11	€ 1.77	€ 0.62	€ 16.72
Dapagliflozin 10 mg	98 FCT	€ 237.65	€ 1.77	€ 0.00	€ 235.88
Dulaglutuide 1.5 mg	12 SFI	€ 287.75	€ 1.77	€ 15.30	€ 270.68
Dulaglutuide 4.5 mg	12 SFI	€ 287.75	€ 1.77	€ 15.30	€ 270.68
Empagliflozin 10 mg	100 FCT	€ 238.35	€ 1.77	€ 12.57	€ 224.01
Empagliflozin 25 mg	100 FCT	€ 191.05	€ 1.77	€ 9.95	€ 179.33
Human insulin (mixed insulin) 100 I.U./ml[6]	3,000 I.U.	€ 89.98	€ 1.77	€ 6.22	€ 81.99
Human insulin (NPH insulin) 100 I.U./ml[6]	3,000 I.U.	€ 89.98	€ 1.77	€ 6.22	€ 81.99
Human insulin (bolus insulin) 100 I.U./ml[6]	3,000 I.U.	€ 89.98	€ 1.77	€ 6.22	€ 81.99
Liraglutide 18 mg	100 - 150 SD	€ 699.15	€ 1.77	€ 38.08	€ 659.30
Abbreviations: SD = single doses; U. = units; I.U. = international units FCT = film-coated tablets; SFI = solution for injection					

LAUER-TAXE® last revised: 1 February 2025

[6] Fixed reimbursement rate

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be 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.

It is assumed that blood glucose self-checks are carried out 1 - 3 times a day if the metabolic situation is stable. Due to the selective SHI agreements on blood glucose test strips, lancets and disposable needles, the corresponding costs are calculated on the basis of the cheapest pack in each case and reported on the basis of the pharmacy sales price level.

Designation of the therapy	Designation	Cost/ pack[7]	Number	Consumption/ year
Medicinal product to be assessed				
Insulin icodec	Blood glucose test strips	€ 17.95	1 - 3 x every 7 days	52.1 - 156.3
	Lancets	€ 4.20	1 - 3 x every 7 days	52.1 - 156.3
Concomitant active ingredient of the medicinal product to be assessed				
Human insulin (Bolus insulin)	Blood glucose test strips	€ 17.95	3 x daily	1,095
	Lancets	€ 4.20	3 x daily	1,095
	Disposable needles	€ 13.00	3 x daily	1,095
Liraglutide	Disposable needles	€ 13	1 x daily	365
Appropriate comparator therapy				
Human insulin (NPH insulin)	Blood glucose test strips	€ 17.95	1 - 3 x daily	365 - 1,095
	Lancets	€ 4.20	1 - 3 x daily	365 - 1,095
	Disposable needles	€ 13.00	1 - 2 x daily	365 - 730
Conventional insulin therapy (CT, mixed insulin)	Blood glucose test strips	€ 17.95	1 - 3 x daily	365 - 1,095
	Lancets	€ 4.20	1 - 3 x daily	365 - 1,095
	Disposable needles	€ 13.00	1 - 2 x daily	365 - 730
Intensified insulin therapy (ICT)	Blood glucose test strips	€ 17.95	4 - 6 x daily	1,460 - 2,190
	Lancets	€ 4.20	4 - 6 x daily	1,460 - 2,190
	Disposable needles	€ 13.00	4 - 5 x daily	1,460 - 1,825
Liraglutide	Disposable needles	€ 13	1 x daily	365

[7] 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 February 2025.

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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or

- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with

different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a1) Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current medicinal therapy consisting of at least two hypoglycaemic agents, in addition to diet and exercise, and for whom there is an indication for an insulin therapy

The designated medicinal products concern in each case 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. According to the requirements in the product information, this therapeutic application is a combination that can be used in patients with type 2 diabetes mellitus with oral anti-diabetics, GLP-1 receptor agonists and bolus insulin.

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

References:
Product information for insulin icodec (Awiqli); Awiqli® 700 units/ml solution for injection in pre-filled pen; last revised: May 2024

a2) Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease, who have not achieved adequate glycaemic control with their current medicinal therapy consisting of at least two hypoglycaemic agents, in addition to diet and exercise, and for whom there is an indication for insulin therapy

The designated medicinal products concern in each case 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. According to the requirements in the product information, this therapeutic application is a combination that can be used in patients with type 2 diabetes mellitus with oral anti-diabetics, GLP-1 receptor agonists and bolus insulin.

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

References:
Product information for insulin icodec (Awiqli); Awiqli® 700 units/ml solution for injection in pre-filled pen; last revised: May 2024

b1) Insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous insulin regime, in addition to diet and exercise

The designated medicinal products concern in each case 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. According to the requirements in the product information, this therapeutic application is a combination that can be used in patients with type 2 diabetes mellitus with oral anti-diabetics, GLP-1 receptor agonists and bolus insulin.

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

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Product information for insulin icodec (Awiqli); Awiqli® 700 units/ml solution for injection in pre-filled pen; last revised: May 2024

b2) Insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous insulin regime, in addition to diet and exercise

The designated medicinal products concern in each case 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. According to the requirements in the product information, this therapeutic application is a combination that can be used in patients with type 2 diabetes mellitus with oral anti-diabetics, GLP-1 receptor agonists and bolus insulin.

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

References:
Product information for insulin icodec (Awiqli); Awiqli® 700 units/ml solution for injection in pre-filled pen; last revised: May 2024

Supplement to Annex XIIa of the Pharmaceuticals Directive

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 and provided with patient-group-related information on the period of validity of the designation.

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 9 August 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 11 June 2024.

On 29 August 2024, the pharmaceutical company submitted a dossier for the benefit assessment of insulin icodec to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 30 August 2024 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 insulin icodec.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 November 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 December 2024. The deadline for submitting statements was 23 December 2024.

The oral hearing was held on 6 January 2025.

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 11 February 2025, and the proposed draft resolution was approved.

At its session on 20 February 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	9 August 2022	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	11 June 2024	New determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	6 January 2025	Information on statements received, conduct of the oral hearing
Working group Section 35a	15 January 2025 5 February 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 February 2025	Concluding discussion of the draft resolution
Plenum	20 February 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 February 2025

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

Prof. Hecken