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
Insulin icodec (type 1 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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the

statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 1 diabetes mellitus in adults.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with type 1 diabetes mellitus

Appropriate comparator therapy for insulin icodec:

- Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin degludec, insulin aspart, insulin glulisine, insulin lispro)

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.

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

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.

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

on 1. In addition to insulin icodec, human insulin and insulin analogues (insulin detemir, insulin glargine, insulin degludec, insulin aspart, insulin glulisine, insulin lispro) are approved for the treatment of adults with type 1 diabetes mellitus.

on 2. In the present therapeutic indication, no non-medical measures are considered as the appropriate comparator therapy.

on 3. The following resolution of the G-BA on the benefit assessment according to Section 35a SGB V (Annex XII to the Pharmaceuticals Directive) is available for the therapeutic indication considered here:
- Insulin degludec (resolution of 16 October 2014)

In addition, the following resolution of the G-BA on an amendment to the guideline on investigation and treatment methods used by SHI-accredited physicians:
- Continuous interstitial glucose measurement with real-time measuring devices (rtCGM) for therapy management in patients with insulin-dependent diabetes mellitus (resolution of 16 June 2016)

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 for determining the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

According to the S3 guideline "Therapy of type 1 diabetes" and the joint statement of the German Society of General Practice/Family Medicine (DEGAM), the German Diabetes Society (DDG) and the German Society of Endocrinology (DGE), the best possible imitation of insulin secretion in healthy people is the treatment standard in the therapy of clinically manifest type 1 diabetes mellitus. To maintain normal glucose homeostasis, human insulins (normal insulins or human insulins with a delayed onset of action) or insulin analogues (short-acting or long-acting) should be used to treat subjects with type 1 diabetes mellitus.

According to the S3 guideline, intensified conventional insulin therapy (ICT) is the treatment standard for subjects with type 1 diabetes mellitus. ICT involves substituting the basal insulin requirement with a long-acting insulin (basal insulin) and the prandial insulin requirement with a short-acting insulin (bolus insulin) at mealtimes as well as for correction of elevated glucose levels. Conventional insulin therapy (CT) is mentioned as another therapy option. However, this form of insulin therapy is a subordinate therapy option compared to ICT and is considered, among others, for subjects who are unable to fulfil the requirements of ICT due to cognitive impairments, illness or age.

In addition, insulin pump therapy can be another therapy option if individual therapeutic goals are not achieved or in the case of frequent hypoglycaemias or recurrent severe hypoglycaemias under ICT.

Against the background of the proven benefit by influencing patient-relevant endpoints such as diabetes-related microvascular complications with human insulin, and in view of the lower risk of (nocturnal) hypoglycaemias with insulin analogues, human insulin and insulin analogues are considered as equally appropriate therapy options for the treatment of type 1 diabetes mellitus. In the therapy of type 1 diabetes mellitus, these insulins are used in particular in the form of ICT.

In the overall assessment, human insulin or insulin analogues (insulin detemir, insulin glargine, insulin degludec, insulin aspart, insulin glulisine, insulin lispro) therefore represent the appropriate comparator therapy.

The unchanged continuation of inadequate therapy for type 1 diabetes mellitus, when there is still the option of optimising insulin therapy, does not correspond to the appropriate comparator therapy.

The marketing authorisations and product information for the medicinal products of the appropriate comparator therapy must be observed.

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:

Adults with type 1 diabetes mellitus

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of insulin icodec for the treatment of adults with type 1 diabetes mellitus, the pharmaceutical company used the randomised, open-label, multicentre ONWARDS 6 study.

ONWARDS 6 study

The randomised, open-label, multicentre ONWARDS 6 study investigated the administration of insulin icodec in 582 adults with type 1 diabetes mellitus versus insulin degludec, in each case in combination with insulin aspart. The treatment phase lasted 52 weeks overall. Adults who had been diagnosed with type 1 diabetes mellitus at least one year prior to enrolment in the study and who had also been receiving therapy with multiple daily insulin injections (regimen with basal and bolus insulin analogues) for one year were enrolled in the study. Insulin-naive subjects were not examined. The HbA1c value should be less than 10%. The patients were randomised at the start of the study in a 1:1 ratio to the two study arms. According to the study design, all study participants were to enter a 26-week extension phase after a 26-week main phase. The study was conducted between April 2021 and December 2022.

Medicinal therapy and implementation of the appropriate comparator therapy

In the ONWARDS 6 study, the study participants received intensified insulin therapy (ICT) at the start of the study with either the insulin icodec to be administered once a week or the insulin degludec to be administered once a day, in each case in combination with insulin aspart as a bolus insulin. Treatment with the respective basal insulin was carried out using a fixed titration algorithm based on three consecutive fasting plasma glucose values. The dose of bolus insulin at the start of the study was determined on the basis of the dose of existing bolus insulin therapy at the time of enrolment in the study and should be kept stable during the first 8 weeks of the study. For safety reasons, dose adjustments were nevertheless permitted within this period. After the first 8 weeks, adjustments could be made once a week depending on the self-measured plasma glucose value according to a fixed titration algorithm with the help of the principal investigator or, if possible and according to the principal investigator's assessment, also based on a carbohydrate count. The titration algorithm for insulin icodec and insulin degludec used in the study, and the specification of the fixed dosage of insulin aspart in the first 8 weeks did not correspond to the requirements in the respective product information.

In both study arms, the dosages of basal and bolus insulin were to be titrated on the basis of a target value range for fasting blood glucose (80 to 130 mg/dl). Deviations from the titration algorithm were only permitted due to safety concerns and had to be documented and justified by the principal investigator. The blood glucose values were measured by the patients themselves and, based on this, the insulin dose was adjusted according to the titration algorithm described and, if applicable, hypoglycaemias were assessed. In addition, blood

glucose levels were monitored and collected using a CGM[2] system (Dexcom G6). According to the study design, self-measurement should be performed for hypoglycaemic episodes collected by the CGM. If a plasma glucose (PG) value outside the target range (< 70 mg/dl) is confirmed during self-measurement, the hypoglycaemia should be assessed as an event in the electronic diary and carbohydrates should be administered and dose adjustments made to the hypoglycaemic therapy.

Overall, the ICT used is considered to be an adequate implementation of the determined appropriate comparator therapy. With regard to the lack of possibility of patient-individual dose adjustments by the specified titration algorithm in the ONWARDS 6 study, which do not correspond to the current recommendations, uncertainties remain as to whether the study results can be transferred to the German healthcare context ~~without restriction~~.

Extent and probability of the additional benefit

Mortality

One death occurred in the intervention arm of the ONWARDS 6 study. For the endpoint of overall mortality, there was no statistically significant difference between the treatment arms of the ONWARDS 6 study.

Morbidity

HbA1c value

The HbA1c value is used to determine the percentage of glycated haemoglobin in the patient's blood. The HbA1c value is regarded as a sufficiently valid surrogate for microvascular secondary diseases in the therapeutic indication of type 1 diabetes mellitus.

For the change in the HbA1c value compared to baseline, there was a statistically significant difference to the disadvantage of insulin icodec compared to insulin degludec (in each case in combination with insulin aspart). However, this effect is considered irrelevant, as the 95% confidence interval of the effect with the lower limit of 0.02% is close to the zero effect.

The European Medicines Agency (EMA) used a threshold of 0.3 percentage points for the HbA1c value to assess the non-inferiority of insulin icodec compared to insulin degludec. Non-inferiority could be proven for insulin icodec at week 26; it was not proven at week 52.

Acute coronary syndrome, cerebrovascular events, heart failure

For the endpoints of acute coronary syndrome, cerebrovascular events and heart failure, the ONWARDS 6 study showed no statistically significant difference between the treatment arms in each case.

Diabetic retinopathies, end-stage renal disease

For the endpoints of diabetic retinopathies and end-stage renal disease, no evaluations of suitable operationalisation are available in each case.

Quality of life

In the ONWARDS 6 study, health-related quality of life was not assessed.

[2] CGM: Continuous Glucose Monitoring

Side effects

Serious adverse events (SAEs) and therapy discontinuation due to adverse events (AEs)

For the endpoints of SAEs and therapy discontinuation due to AEs, there were no statistically significant differences between the treatment arms of the ONWARDS 6 study.

Hypoglycaemias

For the benefit assessment, the pharmaceutical company presented various analyses on hypoglycaemias, some of which were conducted *post hoc* for the dossier:

For the endpoints of *non-severe symptomatic, confirmed hypoglycaemias (PG < 54 mg/dl or PG < 70 mg/dl)*, the pharmaceutical company presented post hoc analyses in the dossier or in the statement. However, according to the information provided by the pharmaceutical company, the symptoms may not have been fully collected by all study participants or principal investigators during the study, although this was intended according to CRF[3]. However, there are no suitable data available for non-severe symptomatic, confirmed hypoglycaemias since only symptomatic hypoglycaemias are used for the benefit assessment and no systematic assessment of symptomatology was carried out in the present case.

For the endpoint of *severe hypoglycaemias*, *post hoc* analyses are available. Severe hypoglycaemias were operationalised as follows: They required the assistance of healthcare professionals for treatment with glucagon or glucose IV; were life-threatening; resulted in hospitalisation or were characterised by severe neuroglycopenic symptoms.
For the endpoint of severe hypoglycaemias, there were no statistically significant differences between the treatment arms of the ONWARDS 6 study.

With regard to the endpoint of *severe hypoglycaemias (PT[4] hypoglycaemia)*, the ONWARDS 6 study showed a statistically significant difference to the disadvantage of insulin icodec compared to insulin degludec (in each case in combination with insulin aspart).

In the dossier, the pharmaceutical company also presented a *post hoc* evaluation of hypoglycaemias, which includes a collection of PTs based on SAEs. This evaluation is not used for the benefit assessment as it cannot be ruled out by the *post hoc* selection of PTs that the compilation was results-driven.

Diabetic ketoacidoses

For the endpoint of diabetic ketoacidoses, there was no statistically significant difference between the treatment arms of the ONWARDS 6 study.

Overall assessment

For the benefit assessment of insulin icodec in adults with type 1 diabetes mellitus, data are available from the ONWARDS 6 study, which investigated the administration of insulin icodec versus insulin degludec, in each case in combination with insulin aspart as part of an intensified insulin therapy. Data are available on various endpoints from the endpoint categories of mortality, morbidity and side effects after a treatment duration of 52 weeks.

For the endpoint of overall mortality, there was no statistically significant difference between the treatment arms of the study.

[3] CRF: case report form
[4] PT: Preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA)

With regard to morbidity, there was a statistically significant disadvantage for the change in the HbA1c value compared to baseline with insulin icodec compared to insulin degludec (in each case in combination with insulin aspart); however, a relevant effect cannot be assumed with sufficient certainty in the present case.
For the other endpoints in the morbidity category, there were no statistically significant differences (acute coronary syndrome, cerebrovascular events and heart failure) or no evaluations of a suitable operationalisation were available (diabetic retinopathies, end-stage renal disease).

Endpoints on health-related quality of life were not assessed in the ONWARDS 6 study.

For the side effects, there were no statistically significant differences between the treatment arms in the overall rates of serious adverse events (SAEs) and therapy discontinuation due to AEs. In detail, however, there was a negative effect for the specific AE of serious hypoglycaemias; the percentage of patients with serious hypoglycaemias is in the low single-digit percentage range. With regard to non-severe symptomatic, confirmed hypoglycaemias (blood glucose limit value of ≤ 54 mg/dl or ≤ 70 mg/dl), there were no evaluations of a suitable operationalisation. For severe hypoglycaemias, there were no statistically significant differences between the treatment groups. Overall, based on the data from the ONWARDS 6 study, a disadvantage was identified in the side effects category for insulin icodec compared to insulin degludec, as the negative effect in the endpoint of serious hypoglycaemias, which can have a potentially fatal course, is of particular relevance for patients with type 1 diabetes mellitus.

Overall, there were neither advantages nor disadvantages of insulin icodec compared to insulin degludec in the endpoint categories of mortality and morbidity. Health-related quality of life was not assessed in the ONWARDS 6 study. For the side effects, however, there was a disadvantage with insulin icodec in detail for the specific AE of serious hypoglycaemias, which can have a potentially fatal course. In the overall assessment of the study results, however, the derivation of a lower benefit of insulin icodec does not appear justified. In summary, it is therefore concluded that, based on the results of the ONWARDS 6 study, the additional benefit of insulin icodec compared with insulin degludec, in each case in combination with insulin aspart as part of an intensified insulin therapy, is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Awiqli" with the active ingredient "insulin icodec". The therapeutic indication assessed here is as follows: Adults with type 1 diabetes mellitus.

Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin degludec, insulin aspart, insulin glulisine, insulin lispro) were determined by the G-BA as the appropriate comparator therapy.

For the benefit assessment of insulin icodec, the pharmaceutical company presented the data from the ONWARDS 6 study, which investigated the administration of insulin icodec versus insulin degludec, in each case in combination with insulin aspart as part of an intensified insulin therapy.

For the endpoint of overall mortality, there was no statistically significant difference between the treatment arms of the study.

With regard to the morbidity category, there were no relevant differences in the endpoints or no evaluations of a suitable operationalisation were available.

Endpoints on health-related quality of life were not assessed in the ONWARDS 6 study.

For the side effects, there were no statistically significant differences between the treatment arms in the overall rates of serious adverse events (SAEs) and therapy discontinuation due to AEs. In detail, however, there was a negative effect for the specific AE of serious hypoglycaemias. For the endpoint category of side effects, a disadvantage of insulin icodec compared to insulin degludec is therefore identified, as the negative effect in the endpoint of serious hypoglycaemias, which can have a potentially fatal course, is of particular relevance for patients with type 1 diabetes mellitus.

Due to the lack of patient-individual dose adjustments in the study, uncertainties remain as to whether the study results are fully transferable to the German healthcare context.

The overall assessment of the study results shows that the additional benefit of insulin icodec compared with insulin degludec, in each case in combination with insulin aspart as part of an intensified insulin therapy, 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 pharmaceutical company used the data from the benefit assessment procedure for insulin degludec to determine the number of patients in the SHI target population. These data are based on an evaluation of an IMS Health Disease Analyser study from October 2012 to October 2013, which identified patients who were already receiving a combination therapy consisting of a basal insulin and a bolus insulin.

Overall, the stated patient number is considered to be an underestimate, as in principle all adults with type 1 diabetes mellitus are eligible for insulin therapy and not only those who are already receiving a combination therapy of basal insulin and bolus insulin. It is also questionable to what extent the data from 2012/2013 can still be applied to the current medical treatment situation.

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: 27 January 2025):

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

In patients and patients with type 1 diabetes mellitus treated with insulin icodec, there was an increased risk of hypoglycaemia compared with insulin degludec (see sections 4.8 and 5.1 of the product information for Awiqli). Patients with type 1 diabetes mellitus should only be treated with insulin icodec if a clear benefit is expected from once-weekly dosage. The safety and efficacy of insulin icodec in newly diagnosed insulin-naive patients with type 1 diabetes mellitus have not been established. No data available.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for

medical professionals and patients. The training material[5] contains, in particular, information on the use of insulin icodec for once-weekly administration as well as warnings about the risk of confusion with other insulins.

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 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. In addition, therapy with insulin icodec must be combined with a bolus insulin.

The potency of insulin analogues (insulin icodec, insulin glargine, insulin determir, insulin degludec, insulin aspart, insulin glulisine, insulin lispro) is expressed in units (U.). One U. of insulin analogue 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 dosing scheme used, the amount of insulin and the frequency of application must be individually adjusted according to the physical activity and lifestyle of the subjects. 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 the insulin analogues as well as human insulin (NPH insulin) is shown as "1 - 2 x daily", although the frequency of application may differ for individual subjects. According to the product information[6], the average insulin requirement is often 0.5 - 1.0 I.U. per kg body weight (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"[7].

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

[5] Educational materials for healthcare professionals and patients using the diabetes medicine Awiqli: https://www.ema.europa.eu/en/documents/medication-error/awiqli-measures-intended-reduce-risk-confusion-dosing-requirements_en.pdf [accessed 11 February 2025].

[6] Product information for Insuman® Basal, last revised: July 2020.

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

Adults with type 1 diabetes mellitus

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				
Insulin icodec	Continuously, 1 x every 7 days	52.1	1	52.1
Concomitant active ingredient of the medicinal product to be assessed				
Human insulin (bolus insulin)	Continuously, 3 x daily	365.0	1	365.0
Appropriate comparator therapy				
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
Long-acting insulin analogues				
Insulin degludec	Continuously, 1 x daily	365.0	1	365.0
+ human insulin (bolus insulin)	Continuously, 3 x daily	365.0	1	365.0
Insulin detemir	Continuously, 1 - 2 x daily	365.0	1	365.0
+ human insulin (bolus insulin)	Continuously, 3 x daily	365.0	1	365.0
Insulin glargine	Continuously, 1 x daily	365.0	1	365.0
+ human insulin (bolus insulin)	Continuously, 3 x daily	365.0	1	365.0
Short-acting insulin analogues				
Human insulin (NPH insulin)	Continuously, 1 - 2 x daily	365.0	1	365.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
+ insulin aspart	Continuously, 3 x daily	365.0	1	365.0
Human insulin (NPH insulin)	Continuously, 1 - 2 x daily	365.0	1	365.0
+ insulin glulisine	Continuously, 3 x daily	365.0	1	365.0
Human insulin (NPH insulin)	Continuously, 1 - 2 x daily	365.0	1	365.0
+ insulin lispro	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	Average annual consumption by potency
Medicinal product to be assessed					
Insulin icodec	1.4 U. - 4.2 U./ kg BW	108.78 U. - 326.34 U.	1 x 108.78 U. - 1 x 326.34 U.	52.1 52.1	5,667.44 U. - 17,002.31 U.
Concomitant active ingredient of the medicinal product to be assessed					
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.	365.0 365.0	5,672.10 I.U. - 17,016.3 I.U.
Appropriate comparator therapy					
Intensified insulin therapy (ICT)					
Human insulin (NPH 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	5,672.10 I.U. - 17,016.3 I.U.
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	5,672.10 I.U. - 17,016.3 I.U.
Long-acting insulin analogues					
Insulin degludec	0.2 U. - 0.6 U./ kg BW	15.54 U. - 46.62 U.	1 x 15.54 U. - 1 x 46.62 U.	365.0	5,672.10 U. - 17,016.3 U.
+ human insulin (bolus insulin)	0.2 U. - 0.6 U./ kg BW	15.54 U. - 46.62 U.	1 x 15.54 U. - 1 x 46.62 U.	365.0	5,672.10 U. - 17,016.3 U.
Insulin detemir	0.2 U. - 0.6 U./ kg BW	15.54 U. - 46.62 U.	1 x 15.54 U. - 1 x 46.62 U.	365.0	5,672.10 U. - 17,016.3 U.
+ human insulin (bolus insulin)	0.2 U. - 0.6 U./ kg BW	15.54 U. - 46.62 U.	1 x 15.54 U. - 1 x 46.62 U.	365.0	5,672.10 U. - 17,016.3 U.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Insulin glargine + human insulin (bolus insulin)	0.2 U. - 0.6 U./ kg BW 0.2 U. - 0.6 U./ kg BW	15.54 U. - 46.62 U. 15.54 U. - 46.62 U.	1 x 15.54 U. - 1 x 46.62 U. 1 x 15.54 U. - 1 x 46.62 U.	365.0 365.0	5,672.10 U. - 17,016.3 U. 5,672.10 U. - 17,016.3 U.
Short-acting insulin analogues					
Human insulin (NPH insulin) + insulin aspart	0.2 U. - 0.6 U./ kg BW 0.2 U. - 0.6 U./ kg BW	15.54 U. - 46.62 U. 15.54 U. - 46.62 U.	1 x 15.54 U. - 1 x 46.62 U. 1 x 15.54 U. - 1 x 46.62 U.	365.0 365.0	5,672.10 U. - 17,016.3 U. 5,672.10 U. - 17,016.3 U.
Human insulin (NPH insulin) + insulin glulisine	0.2 U. - 0.6 U./ kg BW 0.2 U. - 0.6 U./ kg BW	15.54 U. - 46.62 U. 15.54 U. - 46.62 U.	1 x 15.54 U. - 1 x 46.62 U. 1 x 15.54 U. - 1 x 46.62 U.	365.0 365.0	5,672.10 U. - 17,016.3 U. 5,672.10 U. - 17,016.3 U.
Human insulin (NPH insulin) + insulin lispro	0.2 U. - 0.6 U./ kg BW 0.2 U. - 0.6 U./ kg BW	15.54 U. - 46.62 U. 15.54 U. - 46.62 U.	1 x 15.54 U. - 1 x 46.62 U. 1 x 15.54 U. - 1 x 46.62 U.	365.0 365.0	5,672.10 U. - 17,016.3 U. 5,672.10 U. - 17,016.3 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.

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					
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					
Human insulin (bolus insulin)[8] 100 I.U./ml	3,000 I.U.	€ 89.98	€ 1.77	€ 6.22	€ 81.99
Appropriate comparator therapy					
Human insulin (NPH insulin)[8] 100 I.U./ml	3,000 I.U.	€ 89.98	€ 1.77	€ 6.22	€ 81.99
Human insulin (bolus insulin)[8] 100 I.U./ml	3,000 I.U.	€ 89.98	€ 1.77	€ 6.22	€ 81.99
Long-acting insulin analogues					
Insulin degludec 100 U./ml	3,000 U.	€ 103.88	€ 1.77	€ 5.12	€ 96.99
Insulin detemir 100 U./ml	3,000 U.	€ 175.79	€ 1.77	€ 9.12	€ 164.90
Insulin glargine 100 U./ml	3,000 U.	€ 89.98	€ 1.77	€ 4.35	€ 83.86
Short-acting insulin analogues					
Insulin aspart 100 U./ml	3,000 U.	€ 89.98	€ 1.77	€ 4.35	€ 83.86
Insulin glulisine 100 U./ml	3,000 U.	€ 124.34	€ 1.77	€ 6.26	€ 116.31
Insulin lispro 100 U./ml	3,000 U.	€ 107.37	€ 1.77	€ 5.32	€ 100.28
Abbreviations: U. = units; I.U. = international units					

LAUER-TAXE® last revised: 1 February 2025

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.

[8] Fixed reimbursement rate

Designation of the therapy	Designation	Costs/ Packaging[9]	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
Appropriate comparator therapy				
Human insulin (NPH insulin) + human insulin (bolus insulin)	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
Long-acting insulin analogues				
Insulin degludec + human insulin (Bolus insulin)	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 x daily	1,460
Insulin detemir + human insulin (Bolus insulin)	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
Insulin glargine + human insulin (Bolus insulin)	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 x daily	1,460
Short-acting insulin analogues				
Human insulin (NPH insulin) + insulin aspart	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
Human insulin (NPH insulin) + insulin glulisine	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

[9] Number of blood glucose 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.

Designation of the therapy	Designation	Costs/ Packaging[9]	Number	Consumption/ year
Human insulin (NPH insulin) + insulin lispro	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

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:

Adults with type 1 diabetes mellitus

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for insulin icodec (Awiqli); Awiqli® 700 units/ml; last revised: May 2024

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.

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.

By letter dated 7 January 2025, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 30 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	6 January 2025 7 January 2025	Information on statements received, conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
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