Gemeinsamer Bundesausschuss

Justification

for 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 Teplizumab (type 1 diabetes mellitus, ≥ 8 years)

From 6 August 2026

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess 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 studies the pharmaceutical company have 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 decide 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 teplizumab on 15 February 2026 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO). Pursuant to 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 of the Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 13 February 2026.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 May 2026 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 teplizumab 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, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA have 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 teplizumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have made 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 teplizumab (Teizeild) in accordance with the product information

Teizeild is indicated to delay the onset of stage 3 type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with stage 2 T1D.

Therapeutic indication of the resolution (resolution of 6 August 2026):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults and children 8 years of age and older with stage 2 type 1 diabetes mellitus (T1D), who do not (yet) have clinically manifest T1D; for delaying the onset of stage 3 T1D

Appropriate comparator therapy for teplizumab:

- Monitoring wait-and-see approach

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 according to 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.

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 they determine 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 for 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 for 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 the therapeutic indication to delay the onset of stage 3 type 1 diabetes mellitus (T1D) in adults and children 8 years of age and older with stage 2 T1D, no medicinal products other than the active ingredient teplizumab are approved.

On 2. A non-medicinal treatment cannot be considered as the appropriate comparator therapy for the indication to be assessed.

On 3. In the therapeutic indication for the treatment of type 1 diabetes mellitus, the following resolutions of the G-BA on the benefit assessment pursuant to Section 35a SGB V are available:
- Insulin degludec (resolution of 16 October 2014)
- Insulin degludec (resolution of 20 August 2015, new therapeutic indication)
- Insulin icodec (resolution of 20 February 2025)

In addition, the following resolution of the G-BA on an amendment to the guideline on SHI-accredited healthcare methods:

- 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 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 indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

The guidelines relevant to this therapeutic indication describe three stages of type 1 diabetes mellitus on the basis of various clinical criteria. Subjects in stages 1 and 2 show no typical symptoms of diabetes and do not yet require treatment. However, the concerned subjects already have diabetes autoantibodies directed against the insulin-producing β-cells of the pancreas. By detecting these antibodies, it is possible to identify subjects in stages 1 and 2 even before the onset of clear clinical symptoms of the disease.

In stage 1, there is a loss of insulin-producing β-cells in the pancreas, although glucose tolerance is still fully preserved (normoglycaemia). In stage 2, dysglycaemia with elevated blood glucose levels[2] is diagnosed. However, treatment is not required in stages 1 and 2. In stage 3, by contrast, glucose homeostasis is disrupted (hyperglycaemia) and symptoms typical of diabetes, such as polyuria, polydipsia and weight loss, occur. It is only at this stage that lifelong treatment involving exogenous insulin administration becomes necessary.

Subjects with stage 3 type 1 diabetes mellitus require continuous insulin treatment to keep their glucose metabolism stable at all times. The current guidelines therefore only include treatment recommendations for clinically manifest, insulin-dependent type 1 diabetes mellitus. However, the guidelines do not make any recommendations for patients with stage 1 and 2 type 1 diabetes mellitus.

This therapeutic indication covers patients who are still without clinically manifest type 1 diabetes mellitus, but who have persistent autoantibodies associated with an FBG level between 100 and 125 mg/dl or an HbA1c level between 5.7% and 6.4%, and who are not insulin-dependent. In accordance with current guidelines, these subjects are classified as having stage 2 type 1 diabetes mellitus.

Apart from teplizumab, there are currently no therapy options with a clinically significant effect on the function of insulin-producing β-cells in the pancreas to delay the onset of stage 3. In the absence of alternative treatments, no specific measures are

[2] Fasting blood glucose (FBG) 100 – 125 mg/dl and/or 2-hour blood glucose (BG) 140 – 199 mg/dl and/or HbA1c 5.7–6.4% or an increase in HbA1c by ≥ 10% (S3 Guideline on the Treatment of Type 1 Diabetes, AWMF registry number: 057-013).

recommended in clinical practice for patients with stage 2 type 1 diabetes mellitus to delay the progression of type 1 diabetes mellitus to stage 3.

On the basis of the generally recognised state of medical knowledge, and taking into account the written statement from the Drugs Commission of the German Medical Association (AkdÄ) and the scientific-medical societies, the G-BA therefore consider it appropriate to determine the monitoring wait-and-see approach as the appropriate comparator therapy in the present therapeutic indication.

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

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO.

2.1.3 Extent and probability of the additional benefit

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

Adults and children 8 years of age and older with stage 2 type 1 diabetes mellitus (T1D), who do not (yet) have clinically manifest T1D; for delaying the onset of stage 3 T1D

Hint of a non-quantifiable additional benefit.

Justification:

The TN-10 study was presented for the assessment of the additional benefit of teplizumab compared with the "monitoring wait-and-see approach" (appropriate comparator therapy) in delaying the progression of stage 2 type 1 diabetes mellitus (T1D) in adults and children 8 years of age and older to stage 3 T1D.

TN-10 study

The double-blind randomised controlled trial TN-10 compared teplizumab with placebo. Adults, adolescents and children 8 years of age and older with stage 2 type 1 diabetes mellitus at baseline were enrolled in the study. The patients who took part in the TN-10 study had previously been part of a cohort from a screening and surveillance study designed to identify subjects with type 1 diabetes mellitus (TN-01 study: TrialNet Pathway To Prevention Study).

According to the inclusion criteria, all adults and children participating in the TN-10 study had to be relatives of at least one subject with type 1 diabetes mellitus and also had to have impaired glucose tolerance. This was defined as: FBG[3] between ≥ 110 mg/dl and < 126 mg/dl, or a 2-hour BG[4] level between ≥ 140 mg/dl and < 200 mg/dl, or a 30-, 60- or 90-minute value following an oGTT[5] ≥ 200 mg/dl. Furthermore, patients had to have at least two diabetes autoantibodies, confirmed by two independent tests.[6] Subjects with clinically manifest type 1 diabetes mellitus were excluded from the study.

[3] FBG: Fasting blood glucose level
[4] 2h BG: 2-hour blood glucose level
[5] oGTT: oral glucose tolerance test
[6] The autoantibodies to be detected were glutamate decarboxylase-65 antibody (GAD65), insulinoma-associated antigen-2 antibody (IA-2A), microinsulin antibody (MIAA), zinc transporter-8 antibody (ZnT8) and/or islet cell antibody (ICA).

A total of 76 subjects aged between 8 and 49.5 years were enrolled in the TN-10 study and randomised in a 1:1 ratio to receive treatment with teplizumab (N = 44) or placebo (N = 32).

In the TN-10 study, the time to onset of stage 3 type 1 diabetes mellitus was assessed as the primary endpoint in the morbidity category. Endpoints in the category of side effects were assessed as secondary endpoints. Endpoints in the category of health-related quality of life were not assessed. For all endpoints assessed, patients were followed up until the primary endpoint was reached or until the end of the study. The end of the study was defined as the point at which 40 subjects in the study had been diagnosed with manifest type 1 diabetes mellitus (primary endpoint).

Differences in patient characteristics between the treatment arms

The characteristics of the patients enrolled in the study differed partly between the treatment arms. The percentage of minor subjects was lower in the intervention arm (66%) than in the comparator arm (81%). There were also differences with regard to the presence of specific diabetes autoantibodies required for enrolment in the study. For example, the percentage of subjects who tested positive for four autoantibodies was 27% in the intervention arm, compared with 44% in the comparator arm. The family relationship of the patients in the study to a subject who already had type 1 diabetes mellitus – siblings or second-degree relatives – also differed between the treatment groups. Furthermore, data from the EPAR show differences in BMI: while the median BMI of those below the age of 18 in the teplizumab arm was 18.0 kg/m^2, it was 21.1 kg/m^2 in the placebo arm. Against this background, it cannot be ruled out that the unevenly distributed patient characteristics across the treatment arms, in particular, the specific diabetes autoantibodies detected and BMI, influenced the onset of clinically manifest type 1 diabetes mellitus.

Uncertainties regarding the study population and the dosage of teplizumab

In clinical practice, most patients with type 1 diabetes mellitus (around 80%) have no relatives, who also have type 1 diabetes mellitus, and therefore no family history of the condition. However, all subjects investigated in the TN-10 study had a family history of the condition. Whether the findings of the TN-10 study can generally be transferred to patients without a family history of the condition remains uncertain.

With regard to the inclusion criteria relating to the detection of impaired glucose tolerance, the specified 30-, 60- and 90-minute values following the oGTT are not in accordance with the guidelines. The 2-hour blood glucose level following an oGTT is considered in accordance with WHO guidelines (this was also used in the study), but the blood glucose levels after 0, 60 and 90 minutes should not be used to diagnose impaired glucose tolerance. It is unclear how many subjects were enrolled on the basis of this non-recommended diagnostic criterion.

Further uncertainties arise from the altered formulation of teplizumab following a change of manufacturer, which led to a different dosage regimen in the TN-10 study compared with the medicinal product that was ultimately approved (a 20% lower cumulative dose of teplizumab in the TN-10 study). Due to a lack of comparator data, it remains unclear whether, and to what extent, the different dosage has an impact on patient-relevant endpoints.

Implementation of the appropriate comparator therapy in the TN-10 study

In the intervention arm, subjects received a 14-day course of treatment with teplizumab as a solution for infusion, while those in the comparator arm received a placebo. At 3, 6 and 12 months, and every 6 months thereafter, physical examinations were carried out, subjects were questioned regarding symptomatology and any side effects, an oGTT was performed, and HbA1c levels were measured. In addition, random blood glucose levels were measured every 3 months when an oGTT was not performed. Overall, the measures carried out in the comparator arm are regarded as an adequate implementation of the appropriate comparator therapy – the monitoring wait-and-see approach. The TN-10 study is therefore being used for the assessment of the additional benefit of teplizumab compared to the monitoring wait-and-see approach.

Extent and probability of the additional benefit

Mortality

There were no deaths in the TN-10 study.

Morbidity

Onset oftype 1 diabetes mellitus

This endpoint was assessed as the primary endpoint and operationalised as the time to diagnosis of clinically manifest type 1 diabetes mellitus. Manifest type 1 diabetes mellitus was defined as meeting one of the following criteria:

- severe hyperglycaemia with acute metabolic decompensation[7],
- clinical symptoms of diabetes[8] and a random BG[9] level ≥ 200 mg/dl (11.1 mmol/l),
- FBG[10] ≥ 126 mg/dl (7.0 mmol/l),
- 2-hour BG[11] level ≥ 200 mg/dl (11.1 mmol/l).

In the case of subjects diagnosed on the basis of diabetes symptoms and a random BG level ≥ 200 mg/dl, or criteria other than those mentioned above, adjudication was carried out by the TrialNet Diabetes Adjudication Committee. It was also possible to make a diagnosis based on other criteria that were not further specified.

The criteria defined using a glucose test are in line with the S3 guidelines. Alternatively, the diagnosis can be made in accordance with the guidelines on the basis of an HbA1c level ≥ 6.5%. Although the HbA1c level was assessed as a diagnostic criterion in a second, revised version of the case report form, it is not clear whether, or from when, the revised questionnaire was used, nor how many subjects were subsequently diagnosed with manifest type 1 diabetes mellitus on the basis of pre-specified criteria other than those mentioned above. Notwithstanding these uncertainties, it is assumed that the events collected for this endpoint do in fact correspond to a diagnosis of manifest type 1 diabetes mellitus.

Overall, no analyses of the individual criteria defined for the primary endpoint are available, making it unclear how many subjects experienced acute metabolic decompensation or diabetic ketoacidosis in accordance with the first criterion for the onset of diabetes. Furthermore, as the study generally ended for subjects with manifest type 1 diabetes mellitus, diabetic ketoacidosis was not assessed until the actual end of the study. Furthermore, the temporal relationship between the diabetes symptoms and a randomly measured elevated blood glucose level is unclear. For this reason, it is not possible to consider the clinical symptoms of manifest type 1 diabetes mellitus as an independent endpoint.

[7] diabetic ketoacidosis was defined as acute metabolic decompensation.
[8] polyuria, polydipsia and unexplained weight loss,
[9] random blood glucose (BG) measurement = regardless of the time elapsed since the last meal,
[10] for the FBG, there must have been no calorie intake for a period of at least eight hours,
[11] The test should be carried out using a glucose load equivalent to 1.75 g/kg body weight, up to a maximum of 75 g of anhydrous glucose dissolved in water.

Despite the uncertainties mentioned in relation to the primary endpoint, the first-time onset of type 1 diabetes mellitus – and thus, the progression of the disease to stage 3, which is associated with the typical clinical symptoms of diabetes and the need for long-term insulin therapy – fundamentally constitutes a patient-relevant endpoint. The results for this endpoint are therefore used for the assessment of the additional benefit.

For the primary endpoint, operationalised as "time to onset of type 1 diabetes mellitus", there was a statistically significant advantage of teplizumab compared with placebo. The median delay in the onset of clinically manifest type 1 diabetes mellitus was two years with teplizumab, compared with placebo.

However, the data from time-to-event analyses show that a marked increase in the incidence of events relating to the onset of type 1 diabetes mellitus occurred as early as 3 to 9 months after the start of the study in subjects in the placebo arm but not in the subjects who received teplizumab. During the marketing authorisation procedure, concerns regarding the high number of early diabetes onset events in the placebo arm, which contradicted the expected natural history of the disease, were also addressed.[12]

Quality of life

In the TN-10 study, no endpoints of the health-related quality of life category were assessed.

Side effects

In the TN-10 study, adverse events (AEs) were collected from the start of the study until the onset of type 1 diabetes mellitus or until the end of the study. Due to the more frequent and earlier onset of type 1 diabetes mellitus in the comparator arm, there are differences in the observation periods. For this reason, the analyses of relative risk (RR) presented in the dossier are unsuitable (with the exception of the endpoint of discontinuation due to AEs); the data submitted subsequently during the written statement procedure are therefore taken into account here.

As the treatment period in each of the two study arms was 14 days, discontinuation due to AEs could only have occurred during this period. For this endpoint, the data from the dossier are taken into account.

Serious adverse events (SAEs)

For the overall rate of SAEs, there was no statistically significant difference between the treatment arms.

Therapy discontinuation due to adverse events (AEs)

For the endpoint of therapy discontinuation due to AEs, the study showed no statistically significant difference between the treatment arms.

[12] Teizeild: EPAR - Scientific conclusion - Divergent positions of CHMP https://www.ema.europa.eu/en/documents/scientific-conclusion/teizeild-epar-scientific-conclusion-divergent-positions-chmp_en.pdf

Severe AEs (CTCAE grade ≥ 3)

For the endpoint of severe AEs, there was a statistically significant disadvantage of teplizumab compared to placebo.

Specific AEs

Infections (AE), serious infections (SAE)

Detailed analysis of the endpoints of infections (AE) and serious infections (SAE) showed no statistically significant difference between the treatment arms in either case.

Severe lymphopenia (AE), skin and subcutaneous tissue disorders (AE)

Detailed analysis of the endpoints of severe lymphopenia (AE) (CTCAE grade ≥ 3) as well as skin and subcutaneous tissue disorders (AE) showed a statistically significant disadvantage of teplizumab compared with placebo for both endpoints.

Overall assessment

The TN-10 study was presented for the assessment of the additional benefit of teplizumab in adults and children 8 years of age and older with stage 2 type 1 diabetes mellitus (T1D) in delaying the onset of stage 3 T1D. The TN-10 study is a double-blind, randomised controlled trial that investigated the 14-day infusion of teplizumab compared with placebo in patients who were relatives of subjects with type 1 diabetes mellitus (stage 2 patients with a family history of the condition). The "time to onset of type 1 diabetes mellitus" endpoint was assessed as the primary endpoint.

There were no deaths in the TN-10 study.

The "time to onset of type 1 diabetes mellitus" endpoint was assessed as the only endpoint in the morbidity endpoint category. The progression of the disease from stage 2 to stage 3 is accompanied by the typical clinical symptoms of type 1 diabetes mellitus and results in a permanent and irreversible dependence on insulin. The onset of type 1 diabetes mellitus is therefore a patient-relevant endpoint. For this endpoint, there was a statistically significant advantage of teplizumab over placebo; teplizumab delayed onset by a median of two years. The extent of the demonstrated advantage of teplizumab in delaying the onset of clinically manifest type 1 diabetes mellitus cannot be conclusively assessed due to methodological limitations in the assessment of this endpoint and the uneven distribution of patient characteristics across the two treatment arms, which could influence the results relating to the onset of type 1 diabetes mellitus.

Furthermore, no additional data on clinical symptoms and other patient-relevant endpoints, such as metabolic decompensation or diabetic ketoacidosis, are available.

Endpoints in the health-related quality of life category were not collected in the study.

For the endpoint of severe AEs (CTCAE grade ≥ 3) in the endpoint category of side effects, there was a statistically significant disadvantage for teplizumab compared with placebo. Detailed analysis of the specific AEs of severe lymphopenia and skin and subcutaneous tissue disorders showed a disadvantage of teplizumab compared with the monitoring wait-and-see approach for each AE.

Overall analysis showed an additional benefit of teplizumab due to its advantage demonstrated for the "onset of type 1 diabetes mellitus" endpoint. However, the extent of this advantage cannot be quantified due to methodological limitations of the study regarding the limited number of investigated subjects and an uneven distribution of patient characteristics across the treatment groups. This is compounded by the fact that a high number of early events of manifest type 1 diabetes mellitus occurred only in the comparator arm, which does not correspond to the expected natural course of the disease. Furthermore, a disadvantage for the endpoint of severe AEs must be taken into account.

Consequently, a non-quantifiable additional benefit of teplizumab in delaying the onset of stage 3 type 1 diabetes mellitus, compared with the monitoring wait-and-see approach, has been identified.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the TN-10 study. Overall, the study has uncertainties that limit the validity of the results.

Whether the findings of the TN-10 study can generally be transferred to patients without a family history of the condition remains uncertain.

Further uncertainties arise regarding the diagnosis of stage 2 T1D, which in some cases deviated from the findings in the guidelines, and regarding the use of teplizumab, which, due to a change in the study dosage, does not correspond to the approved teplizumab dosage.

Furthermore, no data are available on whether, or in how many subjects, metabolic decompensation or diabetic ketoacidosis occurred, as defined by the primary endpoint. Given that the study was, in principle, discontinued prematurely for those patients who had already reached the primary endpoint, the overall significance of the study's results is limited.

Due to the uncertainties described above, the reliability of data is classified under the "hint" category.

2.1.4 Summary of the assessment

This assessment concerns the benefit assessment of the new medicinal product Teizeild, containing the active ingredient teplizumab, which is used in adults, adolescents and children 8 years of age and older with stage 2 type 1 diabetes to delay the onset of stage 3 type 1 diabetes. The G-BA determined the monitoring wait-and-see approach as the appropriate comparator therapy.

The double-blind, randomised controlled trial TN-10, which compared teplizumab with placebo in patients 8 years of age and older with stage 2 type 1 diabetes mellitus, was presented for the benefit assessment. The adults and children taking part in the study were relatives of at least one other subject who already had type 1 diabetes mellitus.

In the mortality endpoint category, there were no deaths during the study.

For the "time to onset of type 1 diabetes mellitus" endpoint in the morbidity endpoint category, there was a statistically significant advantage of teplizumab over placebo; teplizumab delayed the onset by a median of two years. No data are available on clinical symptoms and other patient-relevant endpoints such as diabetic ketoacidosis.

No data were collected in the endpoint category of health-related quality of life.

For the endpoint of severe AEs and, in detail, for severe lymphopenia as well as skin and subcutaneous tissue disorders in the endpoint category of side effects, there was a statistically significant disadvantage of teplizumab compared with placebo.

The overall analysis showed an additional benefit of teplizumab due to its advantage demonstrated for the "onset of type 1 diabetes mellitus" endpoint; however, the extent of this benefit cannot be quantified.

Given the restriction to subjects with a family history of the condition and other uncertainties in the study, the reliability of data is assumed to be, at most, a hint.

In summary, there was a hint of a non-quantifiable additional benefit of teplizumab in delaying the onset of stage type 1 diabetes mellitus stage 3 in subjects 8 years of age and older with stage 2 type 1 diabetes mellitus, compared with the monitoring wait-and-see approach.

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

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

The G-BA take into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainties overall due to methodological limitations. Whilst some of the points of criticism raised in the benefit assessment were addressed by the sources submitted subsequently in the statement, other points of criticism could not be conclusively clarified, e.g. the unverifiable data on the general population and the failure to take uncertainty into account, amongst other things. Overall, the way in which the individual parameters and percentages are combined in the population model's calculation of results is opaque and cannot be interpreted. Consequently, despite the sources provided subsequently, it is not possible to make a definitive assessment of the number of patients in the SHI target population as stated by the pharmaceutical company.

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 Teizeild (active ingredient: teplizumab) at the following publicly accessible link (last access: 18 June 2026):

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

Treatment with teplizumab should be initiated and monitored by experienced specialists.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient card). The training material contains, in particular, information and warnings about possible serious side effects of teplizumab: Cytokine release syndrome, lymphopenia and serious infections.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 June 2026). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

The use of teplizumab is limited to 14 days.

Adults and children 8 years of age and older with stage 2 type 1 diabetes mellitus (T1D), who do not (yet) have clinically manifest T1D; for delaying the onset of stage 3 T1D

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				
Teplizumab	Once on day 1 to 14	14	1	14
Appropriate comparator therapy				
Monitoring wait-and-see approach	Not calculable			

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "2025 Microcensus – body measurements of the population" were applied (adults: average body height: 1.73 m, average body weight: 78.3 kg; 8-year-old child: average body height: 1.34 m, average body weight: 30.7 kg). From this, a body surface area of 1.92 m² is calculated for adults and 1.07 m² for children 8 years of age (calculation according to Du Bois 1916)[13].

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					
Teplizumab	Children 8 years of age and older				
	Day 1: 65 µg/m² Day 2: 125 µg/m² Day 3: 250 µg/m² Day 4: 500 µg/m² Day 5 – 14:	Day 1: 69.6 µg Day 2: 133.8 µg Day 3: 267.5 µg Day 4: 535 µg Day 5 – 14:	Day 1: 1 x 2 mg Day 2: 1 x 2 mg Day 3: 1 x 2 mg Day 4: 1 x 2 mg Day 5 – 14:	1	1 x 2 mg + 1 x 2 mg + 1 x 2 mg + 1 x 2 mg

[13] Federal Health Reporting. Average body measurements of the population (2025, both sexes), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	1,030 µg/m²	1,102.1 µg	1 x 2 mg		+ 10 x 2 mg
	Adults				
	Day 1: 65 µg/m² Day 2: 125 µg/m² Day 3: 250 µg/m² Day 4: 500 µg/m² Day 5 – 14: 1,030 µg/m²	Day 1: 124.8 µg Day 2: 240 µg Day 3: 480 µg Day 4: 960 µg Day 5 – 14: 1,977.6 µg	Day 1: 1 x 2 mg Day 2: 1 x 2 mg Day 3: 1 x 2 mg Day 4: 1 x 2 mg Day 5 – 14: 1 x 2 mg	1	1 x 2 mg + 1 x 2 mg + 1 x 2 mg + 1 x 2 mg + 10 x 2 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. 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					
Teplizumab 2 mg (1 mg/ml)	1 CIS	€ 12,139.56	€ 1.77	€ 690.00	€ 11,447.79
Appropriate comparator therapy					

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
Monitoring wait-and-see approach	Not calculable				
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

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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.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation. According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-apply unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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 their session on 27 February 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. At their session on 2 December 2025, the Subcommittee on Medicinal Products newly determined the appropriate comparator therapy.

On 13 February 2026, the pharmaceutical company submitted a dossier for the benefit assessment of teplizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 16 February 2026 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 teplizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 May 2026, and the written statement procedure was initiated with publication on the G-BA website on 15 May 2026. The deadline for submitting written statements was 5 June 2026.

The oral hearing was held on 22 June 2026.

By letter dated 23 June 2026, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by the IQWiG was submitted to the G-BA on 10 July 2026.

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 were discussed at the Subcommittee's session on 28 July 2026, and the draft resolution was conclusively discussed.

At their session on 6 August 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	27 February 2024	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	2 December 2025	New determination of the appropriate comparator therapy
Working group Section 35a	16 June 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	22 June 2026	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	1 July 2026 15 July 2026	Consultation on the dossier assessment by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	28 July 2026	Concluding discussion of the draft resolution
Plenum	6 August 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 August 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Dr Optendrenk