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 Tisagenlecleucel (reassessment after the deadline: B-cell acute lymphoblastic leukaemia (ALL), relapsed/ refractory, 0 ≤ 25 years)

of 15 February 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA

initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA 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 pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient (Kymriah) to be assessed for the first time on 16 March 2020. For the resolution of 17 September 2020 made by the G-BA in this procedure, a limitation up to 1 September 2023 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of the medicinal product Kymriah recommences when the deadline has expired.

For this purpose, the pharmaceutical company submitted the dossier for the benefit assessment to the G-BA in due time on 31 August 2023 (Section 4, paragraph 3, no. 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO).

Kymriah for the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL) in patients up to and including 25 years of age is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing

authorisation. The extent and probability of the additional benefit are assessed by the G-BA on the basis of the approval studies.

Tisagenlecleucel concerns a gene therapy within the meaning of Section 4, paragraph 9 Medicinal Products Act.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 December 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-01) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tisagenlecleucel.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Tisagenlecleucel (Kymriah) in accordance with the product information

Kymriah is indicated for the treatment of paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

Therapeutic indication of the resolution (resolution of 15.02.2024):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification

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

Justification:

The pharmaceutical company submitted the data from the single-arm ELIANA, ENSIGN and B2001X studies for the new benefit assessment after expiry of the deadline. In the dossier, the pharmaceutical company also conducts an indirect comparison using the propensity score method against retrospective patient-individual data from the German Multicentre Study Group for Adult Acute Lymphoblastic Leukaemia (GMALL) registry, ALL-REZ-BFM registry and the ALL-SCT-BFM registry.

ELIANA study

The ELIANA study is the pivotal approval study for tisagenlecleucel in the present therapeutic indication. The ELIANA study is a single-arm, multicentre and uncontrolled phase II study conducted at 23 study sites worldwide between 2015 and 2022.

Enrolment in the study took place after a screening phase, during which leukapheresis was performed to produce the CAR-T cells. This was followed by a pre-infusion phase lasting several weeks, during which the patients could initially receive one or more bridging chemotherapies. The lymphodepleting chemotherapy had to be completed two to 14 days before the planned tisagenlecleucel infusion.

Of the 98 patients enrolled (ITT population), 83 (94.7%) received bridging chemotherapy and 78 (79.5%) received lymphocyte depletion. In the ELIANA study, the median time between the screening phase, during which leukapheresis took place, and the infusion of tisagenlecleucel was 2.61 months.

80 patients received a tisagenlecleucel infusion (FAS population). Tisagenlecleucel was not infused in 18 patients, mainly due to technical problems (no product release) or death. A total of 31 patients were transferred to the long-term follow-up study LTFU A2205B.

The median age of patients of the ITT population was 11 years. The majority had a Karnofsky/ Lansky performance status of ≥ 80 and a CNS status of 1. Almost all patients had not received prior therapy with blinatumomab or inotuzumab ozogamicin and 40.2% of patients had not undergone prior stem cell transplantation. The patients had undergone a median of 3 previous lines of therapy.

53.8% of patients received subsequent therapy after the tisagenlecleucel infusion. Of these, 22.5% underwent allogeneic stem cell transplantation (alloSCT), with 20% of patients in remission at the time of alloSCT.

Data on mortality, morbidity, quality of life and side effects from the final data cut-off of the ELIANA study from 17 November 2022 are available for the benefit assessment. In addition, a data cut-off of the long-term follow-up study A2205B from 3 May 2022 with data on the endpoint categories of mortality, morbidity and side effects is available. For the benefit assessment, the data cut-off of the ELIANA study from 17 November 2022 is used as well as the data of the long-term follow-up study A2205B from 3 May 2022 for the endpoint category of mortality and the morbidity endpoint of recurrence-free survival (RFS).

ENSIGN study

The ENSIGN study is a single-arm, multicentre and uncontrolled phase II study, which was originally submitted as a supportive study as part of the marketing authorisation procedure. The study was conducted between 2014 and 2019 in 9 study sites in the USA.

The study design essentially corresponds to the ELIANA study. Of the 75 patients enrolled, 66 (88%) received bridging chemotherapy and 61 (81.3%) received lymphocyte depletion. In the ENSIGN study, the median time between the screening phase, during which leukapheresis took place, and the infusion of tisagenlecleucel was 1.7 months.

64 patients received a tisagenlecleucel infusion (FAS population). Tisagenlecleucel was not infused in 11 patients due to technical problems (no product release) or death. A total of 31 patients were transferred to the long-term follow-up study LTFU A2205B.

The median age of patients of the ITT population was 13 years. The majority had a Karnofsky/ Lansky performance status of ≥ 80 and a CNS status of 1. Almost all patients had not received prior therapy with blinatumomab or inotuzumab ozogamicin and 57.3% of patients had not undergone prior stem cell transplantation. The patients had undergone a median of 3 previous lines of therapy.

The total number of patients who received subsequent therapy after the tisagenlecleucel infusion has not been reported. AlloSCT was performed in 12.2% of patients, with 10.8 % of patients in remission at the time of alloSCT.

For the new benefit assessment, the pharmaceutical company submitted the final data cut-off of the study from 24 May 2019 with data on mortality, morbidity and side effects, which had already been submitted in the preliminary procedure. In addition, a data cut-off of the long-term follow-up study A2205B from 3 May 2022 with data on the endpoint categories of mortality, morbidity and side effects is available. For the benefit assessment, the data cut-off of the ENSIGN study from 24 May 2019 is used, as well as the data from the long-term follow-up study A2205B from 3 May 2022 for the endpoint category of mortality and the morbidity endpoint of recurrence-free survival (RFS).

B2001X study

The B2001X study is a single-arm, multicentre, phase IIIb study designed to ensure the possibility of treatment with tisagenlecleucel after completion of the ELIANA and ENSIGN studies. The study was conducted between 2017 and 2020 in 11 study sites in Europe, Canada and Japan.

The study design was similar to the ELIANA and ENSIGN studies described above, with the primary follow-up phase planned for a duration of 12 months from the time of infusion of tisagenlecleucel.

Of the 74 patients enrolled, 62 (83.7%) received bridging chemotherapy and 63 (81.1%) received lymphocyte depletion. The median time between the screening phase, during which

leukapheresis took place, and the infusion of tisagenlecleucel in the B2001X study was 2.46 months.

69 patients received a tisagenlecleucel infusion (FAS population). Tisagenlecleucel was not infused in 5 patients due to technical problems (no product release) or death. A total of 50 patients were transferred to the long-term follow-up study LTFU A2205B following the primary follow-up phase.

The median age of patients of the ITT population was 9.5 years. The majority had a Karnofsky/ Lansky performance status of ≥ 80 and a CNS status of 1. The majority of patients had not received prior therapy with blinatumomab or inotuzumab ozogamicin and 39.2% of patients had not undergone prior stem cell transplantation. The patients had undergone a median of 3 previous lines of therapy.

17.4% of patients received subsequent therapy after the tisagenlecleucel infusion. 2 patients underwent alloSCT (of which n = 1 was in remission).

For the benefit assessment, the pharmaceutical company submits the final data cut-off of the study from 13 October 2020 with data on mortality, morbidity and side effects. In addition, a data cut-off of the long-term follow-up study A2205B from 3 May 2022 with data on the endpoint categories of mortality, morbidity and side effects is available. For the benefit assessment, the data cut-off of the long-term follow-up study A2205B from 3 May 2022 is used for the endpoint category of mortality due to the short follow-up period at the time of the final data cut-off of the B2001X study. For all other endpoints, the final data cut-off of the B2001X study from 13 October 2020 is used, whereby the data from the A2205B study is also taken into account for the morbidity endpoint of recurrence-free survival (RFS).

The external comparator cohort

Retrospective patient-individual data from the GMALL registry and the ALL-REZ-BFM and ALL-SCT-BFM registries were used as an external comparator cohort.

Since 2010, the GMALL registry has included adults with refractory B-cell ALL, with a relapse after alloSCT as well as second or later relapses independent of alloSCT. Data from patients who were enrolled in the registry by September 2017 and had the longest possible follow-up period (at least until the end of 2019; N = 68) were considered. In addition, data from 15 other patients from a previous registry project were considered (total N = 83).

Since 2012, the ALL-REZ-BFM registry has included children and adolescents (< 18 years) with refractory B-Cell-ALL or with a second or later relapse. Data from patients who were enrolled in the registry by September 2017 and had the longest possible follow-up period (at least until the end of 2019; N = 496) were considered.

Between 2003 and 2013, the ALL-SCT-BFM registry enrolled children and adolescents (< 18 years) with relapse after allogeneic stem cell transplantation. The pharmaceutical company considers patients with the longest possible follow-up period (N = 640).

The specific comparator population for the indirect comparison was selected on the basis of inclusion and exclusion criteria, which were based on the clinical studies on tisagenlecleucel (ELIANA and ENSIGN) and had to have undergone at least one line of therapy at the start. According to the protocol of the indirect comparison, no criteria that were not applicable to the comparator population or could not be depicted in the patient data of the registry were included. This meant that inclusion and exclusion criteria, which may be relevant for suitability for CAR-T cell therapy, were not taken into account in some cases.

From the three registries, 302 patient-individual data were included in the external comparator cohort (GMALL = 83; ALL-REZ-BFM = 115; ALL-SCT-BFM = 104). A presentation of baseline characteristics at registry level was not provided by the pharmaceutical company in the dossier, but was subsequently submitted as part of the written statement. In this respect, there are differences in particular in that the comparator cohort has more missing values for the time since initial diagnosis, the number of blasts in the bone marrow and the Karnofsky index. The number of missing values for the cytogenetic surveys and the presence of an extramedullary disease cannot be assessed, as these were assigned to the "no" category in the absence of a data collection. In addition, no data are available for the tisagenlecleucel studies on the time from previous complete remission (CR) to recurrence.

The comparability of the patient populations in terms of time to recurrence after alloSCT is unclear. Only patients who had undergone alloSCT at least 6 months prior to tisagenlecleucel infusion were enrolled in the tisagenlecleucel studies. In its written statement, the pharmaceutical company states that the tisagenlecleucel studies may also enrol patients with a relapse after alloSCT within 6 months, as the inclusion criterion does not refer to enrolment in the study but to the time of the tisagenlecleucel infusion. However, it does not provide data on the percentage of patients with early or late recurrence within the tisagenlecleucel studies and the external comparator cohort.

According to the statements of the scientific-medical societies in the written statement procedure, the time to recurrence after alloSCT is a strong predictive factor, as patients with an early recurrence (< 6 months) have a poor prognosis. During the oral hearing, the German Working Group for Haematopoietic Stem Cell Transplantation and Cellular Therapies (DAG-HSCT) stated with regard to adult patients that in the current healthcare context, the time from alloSCT to recurrence is no longer included as a prognostic factor due to newer immunotherapeutic treatment options. The extent to which this also applies to children and adolescents cannot be conclusively assessed, taking into account the written statement procedure for the present benefit assessment.

With regard to the comparability of the patient populations, it should be noted that inclusion or exclusion criteria, which may be relevant for suitability for CAR-T cell therapy, were not taken into account in some cases and data on specific baseline characteristics are missing. From the G-BA's perspective, it has therefore not been clearly shown whether the comparator cohort formed is (theoretically) equally eligible for CAR-T cell therapy and thus whether the

assumption of positivity between the patient population of the tisagenlecleucel studies and the patient population of the external comparator cohort is fulfilled.

About the methodology of the indirect comparison

In order to identify confounders, the pharmaceutical company conducted a systematic literature research and a subsequent survey of experts to categorise the confounders. The procedure is considered appropriate overall.

The adjustment was carried out using the "Fine Stratification Weights" propensity score procedure with a total of 10 strata and an "Average treatment effect on the treated (ATT)" estimator.

However, not all confounders categorised as "important" and "very important" could be included in the analysis. For example, no data was available in the external comparison cohort for the confounder "secondary diseases after previous therapies". According to the pharmaceutical company's explanations in its written statement, the confounder "early/late recurrence (after initial diagnosis)" was originally to be included in the analysis as a confounder, but less than 80% of patients in each treatment arm had valid values in at least one line of therapy. As a result, the model for calculating the propensity score did not converge and therefore an analysis taking into account all very important and important confounders could not be carried out. In addition, no data were available for the confounder "time since previous complete remission to recurrence" for the tisagenlecleucel studies. During the oral hearing, the pharmaceutical company stated that the required operationalisation of this confounder was not collected within the tisagenlecleucel studies, as the time period refers to the response to the first stem cell transplantation performed, but patients may have received several stem cell transplantations. However, the pharmaceutical company's justification does not appear plausible since < 7% of patients received two stem cell transplantations across the three tisagenlecleucel studies according to the patient characteristics of the study populations.

The time between alloSCT and recurrence was subsequently removed from the list of relevant confounders with an amendment to the study protocol. According to the pharmaceutical company's information in the written statement, this change was made after consultation with the clinical experts. Although the time from stem cell transplantation to the first recurrence is clinically relevant, the prognostic value in the event of a subsequent recurrence or subsequent refractoriness has not been validated. As explained above, the prognostic relevance of this factor for children and adolescents cannot be conclusively assessed in the present benefit assessment procedure. In principle, confounders for which a prognostic relevance has not been clearly validated, but cannot be excluded with sufficient certainty, should be considered for adjustment.

Uncertainties remain, among other things, regarding the categorisation of the confounder "Down syndrome" as "unimportant". The literature indicates that patients with Down syndrome have a poorer prognosis compared to patients without Down syndrome due to an

increased recurrence rate and a high treatment-related mortality due to infections. Only a small number of patients with Down syndrome were enrolled in the tisagenlecleucel studies (≤ 8.1% each). No data is available for the external comparator cohort.

In the overall assessment, it should be noted that there is insufficient confounder adjustment due to the lack of consideration of several confounders classified as "important" or "very important" in the analysis.

In addition, the pharmaceutical company only submits the ATT estimator. This no longer refers to the entire derived comparator population, but to a constructed population that cannot be clearly described and only represents the average treatment effect among the treated subjects. The "average treatment effect (ATE)" is generally relevant for the benefit assessment. However, the pharmaceutical company did not submit this in the context of the written statement procedure either and justified this by stating that only the patient population eligible for tisagenlecleucel was relevant for the indirect comparison. However, the suitability for CAR-T cell therapy should already be operationalised when forming the comparator cohort via the inclusion and exclusion criteria in order to fulfil the assumption of positivity. The justification of the pharmaceutical company is therefore inappropriate.

Conclusion on the indirect comparison presented

The aspects described above regarding the insufficiently demonstrated positivity, the inadequate consideration of confounders classified as "important" and "very important" in the analysis and the use of the ATT estimator mean that the propensity score procedure carried out is assessed as invalid and the resulting effect estimators are assessed as not interpretable. The indirect comparison presented is therefore not used for the present benefit assessment.

On the implementation of conditions for a time limit

According to the justification of the resolution of 17 September 2020, the reason for the time limit was to be able to include further evidence on the long-term effects of tisagenlecleucel for patient-relevant endpoints that could possibly answer the question of a potential cure for patients in the benefit assessment. For this purpose, the pharmaceutical company should submit the final results of the ELIANA study after 5 years for the new benefit assessment as well as examine and present the possibility of an indirect comparison and prospective comparative evidence beyond the label-enabling study.

In the dossier, the pharmaceutical company presents the final data cut-offs of the ELIANA, ENSIGN and B2001X studies as well as the data cut-off of the long-term follow-up study A2205B. In addition, the pharmaceutical company carries out an indirect comparison with German registry data in the dossier and presents the results of the single-arm registry data from the European Society for Blood and Marrow Transplantation (EBMT) and Center for International Blood and Marrow Transplant Research (CIBMTR) registry, which cover a period

of approx. 4 years. The time limit requirements are therefore deemed to have been implemented.

Mortality

In relation to the ITT population, the median survival for the ELIANA study is 47.6 months, for the ENSIGN study 28.5 months and for the B2001X study 54.7 months. The data from the long-term study A2205B are also taken into account here.

With regard to the Kaplan-Meier estimator, there was only a slight change between study month 48 and study month 60 for the ELIANA study. The estimator remains constant for the ENSIGN study.

Due to the single-arm study design, a comparative assessment of mortality is not possible.

Morbidity

Response (CR/CRi)

Response was operationalised in the tisagenlecleucel studies using defined criteria based on the criteria of Cheson et al. 2003. The assessment was carried out by an independent review committee. A response was only categorised as such if it lasted for at least 28 days. Response is the primary endpoint in the ELIANA and ENSIGN studies. With regard to the period for determining the response, a period of 3 months was defined in the ELIANA study and a period of 6 months in the ENSIGN and B2001X studies.

The evaluations are presented additionally. A response within 6 months was observed in 68.4% of patients in the ELIANA study, 60% of patients in the ENSIGN study and 77% of patients in the B2001X study.

MRD remission

A negative MRD status is defined in the present studies as less than $1*10^{-4}$ (<0.01%) mononuclear cells in the bone marrow. The MRD status was determined in patients who showed a previous remission after tisagenlecleucel infusion. The measurement was based on polymerase chain reaction or flow cytometry.

The evaluations are presented additionally. The MRD remission rate was 67.3% (ELIANA), 57.3% (ENSIGN) and 40.5% (B2001X).

Recurrence-free survival (RFS)

Recurrence-free survival (RFS) is defined in the tisagenlecleucel studies as the time from achieving remission (CR/CRi) to recurrence or death from any cause. Recurrence was assessed by an independent review committee based on defined criteria.

The therapeutic indication comprises a very heterogeneous patient population in an advanced, pretreated stage of the disease. Despite this, a curative therapeutic approach is still

assumed for a sufficiently relevant percentage of patients in this therapeutic indication. The RFS endpoint is therefore considered patient-relevant.

For the present resolution, the evaluations of the RFS submitted in the written statement procedure are presented, taking into account the data from the long-term follow-up study A2205B and with censoring of patients at the time of alloSCT.

The median RFS was not reached in the ENSIGN study, in the B2001X study it was 51.4 months and in the ELIANA study 46.8 months.

Due to the single-arm study design, a comparative assessment of RFS is not possible.

Event-free survival (EFS)

The failure of a curative therapeutic approach is fundamentally considered to be patient-relevant. The significance of the EFS endpoint depends on the extent to which the selected individual components are suitable for adequately reflecting the failure of potential cure by a curative therapeutic approach.

Event-free survival (EFS) in the tisagenlecleucel studies is defined as the time from enrolment in the study until recurrence, death from any cause after remission (CR/CRi) or therapy failure. Therapy failure was defined as death, adverse event, lack of efficacy or disease progression, or initiation of a new antineoplastic therapy. A definition of lack of efficacy could not be identified in the study documents.

No data on the qualifying events of the EFS endpoint are available in the dossier. The EFS is therefore not used in the present benefit assessment. Notwithstanding this, due to the single-arm study design, a comparative assessment of the data is not possible.

Health status

The health status was assessed in the ELIANA study using the visual analogue scale (VAS) of the EQ-5D VAS questionnaire. The assessment was only carried out on patients who were at least 8 years old. The data is categorised as unusable as the return rate is below 70%.

<u>Quality of life</u>

Quality of life data were assessed in the ELIANA study using the PedsQL questionnaire. The questionnaire consists of four multi-dimensional scales (physical functioning, emotional functioning, social functioning and school functioning) and 3 summary scores (total score, physical component summary score, psychosocial component summary score).

The assessment was only carried out on patients who were at least 8 years old. The data is categorised as unusable as the return rate is below 70%.

Side effects

Adverse events (AEs) were collected in full from the start of chemotherapy for lymphocyte depletion until study month 12 of the primary follow-up phase. Both after study month 12 and at the transition to the secondary follow-up phase, adverse events were only collected selectively. The follow-up period of the first 12 months was divided into the phases "chemotherapy for lymphocyte depletion", "infusion until study week 8" and "study week 9 to study month 12".

The highest rate of severe AEs (CTCAE grade 3/4) and serious AEs (SAEs) across all three studies occurred in the period between tisagenlecleucel infusion and study week 8 (severe AEs: 83.8% (ELIANA)/ 84.4% (ENSIGN)/ 72.5% (B2001X); SAEs: 67.5% (ELIANA)/ 71.9% (ENSIGN)/ 56.5% (B2001X)). In the subsequent phase up to study month 12, the rate of severe AEs and SAEs was lower (severe AEs: 48% (ELIANA)/ 46.4% (ENSIGN)/ 45% (B2001X); SAEs: 30.7% (ELIANA)/ 37.5% (ENSIGN)/ 31.7% (B2001X)).

Due to the single-arm study design, a comparative assessment of side effects is not possible.

Overall assessment

The final data on mortality, morbidity, quality of life (ELIANA only) and side effects are available from the single-arm, pivotal, approval study ELIANA and the single-arm, supportive studies ENSIGN and B2001X. In the dossier, the pharmaceutical company also presents an indirect comparison of these data with retrospective patient-individual data from the GMALL registry, ALL-REZ-BFM registry and ALL-SCT-BFM registry.

The indirect comparison carried out is assessed as invalid due to insufficiently demonstrated positivity, insufficient consideration of confounders classified as "important" and "very important" in the analysis and the use of the ATT estimator, and the resulting effect estimators are assessed as not interpretable. The indirect comparison presented is therefore not used for the present benefit assessment.

Due to the single-arm study design, a comparative assessment of the endpoints on mortality, morbidity and side effects is not possible. Furthermore, the data on the EQ-5D VAS and health-related quality of life cannot be used due to the low return rates.

In the overall assessment, a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

Significance of the evidence

Data from the single-arm, pivotal study ELIANA and the single-arm, supportive studies ENSIGN and B2001X are available for the benefit assessment.

The presented indirect comparison based on retrospective patient-individual data from the GMALL registry, ALL-REZ-BFM registry and ALL-SCT-BFM registry is unsuitable for the benefit assessment.

An adequate comparison based on the single-arm data is not possible. The reliability of data is assessed as a hint overall.

2.1.3 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient tisagenlecleucel due to the expiry of the limitation of the resolution of 17 September 2020.

Tisagenlecleucel has a marketing authorisation as an orphan drug. The present assessment relates to the indication "Kymriah is indicated for the treatment of paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse".

The pharmaceutical company has submitted the final data cut-offs of the single-arm studies ELIANA, ENSIGN and B2001X as well as an indirect comparison with registry data in accordance with the time limit requirements.

The single-arm data from the ELIANA, ENSIGN and B2001X studies were considered for the benefit assessment. The indirect comparison carried out is not used, as it is not considered valid due to insufficiently demonstrated positivity, insufficient consideration of confounders classified as "important" and "very important" in the analysis and the use of the ATT estimator, and the resulting effect estimators are assessed as not interpretable.

Due to the single-arm design of this study, a comparative assessment is not possible. The reliability of data is assessed as a hint overall.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

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 benefit assessment is based on the information in the dossier of the pharmaceutical company.

The publication by Bhojwani et al. does not state where the upper limit of the percentage value for the B cell line (85%) estimated by the pharmaceutical company comes from or how it was derived. A further uncertainty results from the fact that this percentage value is given for childhood and it therefore remains unclear to what extent it can be transferred to the patient population (up to 25 years) covered by the present therapeutic indication. Uncertainties regarding the percentage values for relapses and refractoriness arise in particular from the transfer of percentage values whose basic population does not relate to B-Cell-ALL, but to other forms of ALL. Furthermore, some of the data is very outdated or relates to regions outside Germany, which means that its transferability to the current

German healthcare context is questionable. In addition, the pharmaceutical company only considers patients with new disease within one year who have relapsed or are refractory to first- and second-line therapy, but neither those who had new disease in previous years and have relapsed or are refractory to a later line of therapy in the year under review nor those likewise covered by this therapeutic indication.

Overall, the patient numbers are subject to uncertainty and tend to be underestimated. Compared to the patient numbers in the resolution of 17 September 2020, the present range represents a better approximation of the SHI target population based on current data and the range for paediatric patients.

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 Kymriah (active ingredient: tisagenlecleucel) at the following publicly accessible link (last access: 5 January 2024):

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

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient emergency card. Training material for all healthcare professionals who will prescribe, dispense, and administer tisagenlecleucel includes instructions for identifying, treating, and monitoring cytokine release syndrome and neurological side effects. It also includes instructions on the cell thawing process, availability of tocilizumab at the point of treatment, provision of relevant information to patients, and full and appropriate reporting of side effects.

The patient training programme should explain the risks of cytokine release syndrome and serious neurologic side effects, the need to report symptoms immediately to the treating physician, to remain close to the treatment facility for at least 4 weeks after infusion of tisagenlecleucel, and to carry the patient emergency card at all times.

Tisagenlecleucel must be used in a qualified treatment facility. For the infusion of tisagenlecleucel in the present therapeutic indication, the quality assurance measures for the use of CAR-T cells in B-cell neoplasms apply (ATMP Quality Assurance Guideline, Annex 1).

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: 15 January 2024).

For the cost representation, one year is assumed for all medicinal products.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Tisagenlecleucel concerns genetically modified, patient's own (autologous) T cells, which are usually obtained by leukapheresis. Since leukapheresis is part of the manufacture of the medicinal product according to Section 4, paragraph 14 Medicinal Products Act, no further costs are incurred in this respect for tisagenlecleucel.

Tisagenlecleucel is listed on LAUER-TAXE®, but is only dispensed to appropriate qualified inpatient treatment facilities, and administered there. Accordingly, tisagenlecleucel is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculations are based on the purchase price of the clinic pack, in deviation from the LAUER-TAXE® data usually taken into account.

Tisagenlecleucel is administered as a single intravenous infusion according to the requirements in the underlying product information.

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				
Tisagenlecleucel	Single dose	1	1	1

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied for patients up to 15 years of age. To calculate the required cell quantity for patients weighing up to 50 kg, an average body weight of 7.6 kg was assumed as the lower range for children under one year of age.[2]

The consumption of vials and infusion bags is presented for tisagenlecleucel according to the requirements in the product information. These are administered to the patient in a single infusion depending on the number of cells per vial or infusion bag. The annual treatment costs of tisagenlecleucel are independent of the specific number of vials or infusion bags used.

[2] Federal Statistical Office, Wiesbaden 2018: http://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
Medicinal product to be assessed					
Tisagenlecleucel					
	Body weight up to 50 kg 0.2 bis 5 x 10^6 CAR-positive viable T cells/ kg	Body weight up to 50 kg 1.52 x 10^6 to 2.5 x 10^8 CAR-positive viable T cells	1 or several infusion bags	1	1 or several infusion bags
	Body weight over 50 kg 0.1 to 2.5 x 10^8 CAR-positive viable T cells	Body weight over 50 kg 0.1 to 2.5 x 10^8 CAR-positive viable T cells	1 or several infusion bags	1	1 or several infusion bags

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 fixed reimbursement rates 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)	Value added tax	Costs after deduction of statutory rebates
Medicinal product to be assessed				
Tisagenlecleucel	1 single infusion bag	€ 239,000.00	0[3]	€ 239,000.00

LAUER-TAXE® last revised: 15 January 2024

[3] The medicinal product is exempt from VAT at the applied LAUER-TAXE® last revised.

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.

Prophylactic premedication

Antipyretic and antihistamine premedication is only recommended in the product information of tisagenlecleucel.

Conditioning chemotherapy for lymphocyte depletion

For tisagenlecleucel, provided the white blood cell count is not below ≤ 1,000 cells/µl one week prior to infusion, a treatment regimen for lymphocyte depletion, consisting of intravenous administration of fludarabine (30 mg/m^2) daily over 4 days and cyclophosphamide (500 mg/m^2) daily over 2 days starting with the first fludarabine dose, with tisagenlecleucel infusion administered 2 to 14 days after the start of lymphocyte depletion. For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied for patients up to 15 years of age. This results in an average body surface area of 0.36 m^2 for children under 1 year of age (average body height: 0.67 m; average body weight: 7.6 kg).[2] For patients aged 15 years and older, the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were used as a basis. This results in an average body surface area of 1.90 m^2 for young adult patients aged 25 years (average body height: 1.74 m; average body weight: 75.2 kg; calculation according to Du Bois 1916).[4]

[4] Federal Statistical Office, Wiesbaden 2021: http://www.gbe-bund.de/

Screening for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV)

Patients should be tested for hepatitis B, hepatitis C and HIV infection prior to starting treatment with tisagenlecleucel. The corresponding costs for additionally required SHI services are presented in the resolution.

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	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed							
Tisagenlecleucel							
Conditioning chemotherapy for lymphocyte depletion							
Fludarabine 30 mg/m² = 10.8 mg – 57 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	4.0	€ 445.80 - € 891.60
Cyclophosphamide 500 mg/m² = 180 mg – 950 mg	1 PSI at 500 mg	€ 23.50	€ 2.00	€ 1.54	€ 19.96	2.0	€ 39.92 - € 55.22
	1 PSI at 1000 mg	€ 30.68	€ 2.00	€ 1.07	€ 27.61		
Screening for HBV, HCV and HIV							
Hepatitis B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1.0	€ 9.80
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.45	1.0	€ 4.45
Abbreviations: CII = concentrate for injection or infusion solution; PSI = powder for the preparation of an infusion solution							

LAUER-TAXE® last revised: 15 January 2024

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 drugs 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-use 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

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 information 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:

Children, adolescents and young adults up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse

- 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 tisagenlecleucel (Kymriah); Kymriah 1.2 × 10^6 to 6 × 10^8 cells infusion dispersion; last revised: April 2023

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

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

The benefit assessment of the G-BA was published on 1 December 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 22 December 2023.

The oral hearing was held on 8 January 2024.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 26 January 2024.

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 6 February 2024, and the proposed resolution was approved.

At its session on 15 February 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 November 2023	Information of the benefit assessment of the G-BA
Subcommittee Medicinal products	8 January 2024	Information on written statements received, conduct of the oral hearing
Subcommittee Medicinal products	8 January 2024	Conduct of the oral hearing
Working group Section 35a	17 January 2024 31 January 2024	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	6 February 2024	Concluding discussion of the draft resolution
Plenum	15 February 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 February 2024

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

Prof. Hecken