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 Brexucabtagen Autoleucel (new therapeutic indication: relapsed or refractory B-cell precursor acute lymphoblastic leukaemia, 26 years of age and above)

of 16 March 2023

Contents

1. Legal basis

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

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 online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient brexucabtagen autoleucel (Tecartus) was listed for the first time on 15 March 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 2 September 2022, brexucabtagen autoleucel received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

Tecartus for the treatment of adults 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and 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 on the basis of the approval studies by the G-BA.

On 30 September 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on brexucabtagen autoleucel with the new therapeutic indication relapsed or refractory B-cell precursor ALL in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

Brexucabtagen autoleucel 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 02 January 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 has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs

and patient numbers (IQWiG G22-34) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering 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 brexucabtagen autoleucel.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Brexucabtagen Autoleucel (Tecartus) according to the product information

Tecartus is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

Therapeutic indication of the resolution (resolution of 16 March 2023):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Adults 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)

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

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

Justification:

The pharmaceutical company submitted data from the single-arm, open-label phase I/II ZUMA-3 study for the assessment of the additional benefit of brexucabtagen autoleucel in the therapeutic indication relapsed or refractory B-cell precursor ALL. In addition, the pharmaceutical company presented an indirect comparison without a bridge comparator with data from the retrospective cohort study SCHOLAR-3 in the dossier.

ZUMA-3 study

The ZUMA-3 study is a single-arm phase I/II study to investigate the efficacy and safety of brexucabtagen autoleucel in adults with relapsed or refractory B-cell precursor ALL. The ongoing study started in 2016 has been conducted at a total of 32 study sites across North America and Europe.

23 patients were enrolled in phase I and 58 patients in phase II of the ZUMA-3 study.

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

The study treatment included pretreatment in both phase I and phase II, which included leukapheresis, bridging chemotherapy and, if necessary, cytokine release syndrome prevention. Patients then received conditioning chemotherapy and the brexucabtagen autoleucel infusion. Primary follow-up lasted 24 months and long-term follow-up up to 15 years after infusion. A patient was considered enrolled if leukapheresis was performed.

Patients 18 years of age and above with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, whose disease was primarily refractory or who were in first relapse or relapse after two or more lines of systemic therapy were enrolled in the ZUMA-3 study. Subjects with Philadelphia chromosome-positive disease were eligible for enrolment in the study if they were intolerant to tyrosine kinase inhibitor therapy or had relapsed or refracted after tyrosine kinase inhibitor therapy.

For the benefit assessment, the relevant sub-population of patients 26 years of age and above according to the approved therapeutic indication was considered.

The primary endpoint of the ZUMA-3 study was the incidence of adverse events in phase I and the overall complete remission (patients with complete remission (CR) and with complete remission with incomplete haematological recovery (CRi)) in phase II. Secondary endpoints included overall survival, duration of response, MRD negativity, overall CR rate and allogeneic stem cell transplant rate.

The primary analysis (data cut-off of 9 September 2020) and the data cut-off on the median follow-up time of 21 months (data cut-off of 23 July 2021) are available at this time. For the benefit assessment, the data cut-off with the longest follow-up period of 23 July 2021 was taken into account.

SCHOLAR-3 study

For an indirect comparison on efficacy, the pharmaceutical company presents the SCHOLAR-3 study, which is based on historical data from clinical studies on medicinal products.

For the creation of the external comparison population, a systematic search for clinical studies in the present therapeutic indication was conducted in relevant study registers. 13 matching studies were identified that were conducted between 2010 and 2017 and represented phase I, phase I/II, phase II and phase III studies. A total of 510 patients were enrolled in the 13 identified studies for which patient-level data were available in the "Medidata Enterprise Data Store" (MEDS) database. From these 510 patients, a comparison population of 260 patients was formed using inclusion and exclusion criteria.

For the indirect comparison, two patient pools were formed, from which "synthetic control arms" (SCA-1, SCA-2, SCA-3) were constructed in the further process, whereby a distinction was made between blinatumomab treatment-naive or pretreated patients. The data pool for SCA-1 includes patients who are blinatumomab and inotuzumab ozogamicin treatment-naive and who received a chemotherapy regimen (N = 110) or blinatumomab or inotuzumab ozogamicin (N = 80) during the course of the study.

The data pool for SCA-2 includes, on the one hand, patients who were blinatumomab and inotuzumab ozogamicin treatment-naive at the time of enrolment in the study, who failed blinatumomab or inotuzumab ozogamicin treatment in the course of treatment and who subsequently received a chemotherapy regimen as treatment (N = 50), as well as patients who failed blinatumomab or inotuzumab ozogamicin treatment at the time of enrolment and who

received either a chemotherapy regimen, blinatumomab or inotuzumab ozogamicin in the course of the study (N = 10).

Of the 510 patients originally identified, 190 were enrolled in the SCA-1 study pool and 60 in the SCA-2 study pool. After excluding patients under 26 years of age, 138 patients remained in the SCA-1 study pool and 36 in the SCA-2 study pool. In addition, a combined synthetic control arm was created (N=52). The specific composition of the SCA-3 is not clear from the documents submitted. It can be assumed that this is made up of the patients from SCA-1 and SCA-2 who were included in analyses of overall survival in relation to the full analysis set (FAS) population (SCA-1: N = 20, SCA-2: N = 32).

Indirect comparison between ZUMA-3 and SCHOLAR-3

For the indirect comparison between the ZUMA-3 and SCHOLAR-3 studies, comparative analyses for the phase II population of the ZUMA-3 study (N = 58) with the synthetic control arms SCA-1 (N = 138), SCA-2 (N = 36) and SCA-3 (N = 52) of the SCHOLAR-3 study on the endpoints "overall survival", "overall complete remission", "complete remission", "rate of alloSCT", and "relapse-free survival" are presented by the pharmaceutical company.

Due to the heterogeneity of the available patient populations, propensity score matching was performed for adjustment, taking into account the following covariates: Age at baseline, sex, ECOG performance status, Philadelphia chromosome status, percentage of bone marrow blasts at baseline, number of prior therapies, presence of extramedullary disease at baseline, prior allogeneic stem cell transplantation and primary refractory status. It is unclear how these potential confounders have been identified. A systematic research of potential confounders was not submitted by the pharmaceutical company. The ambiguities regarding the procedure for selecting potential confounders could not be resolved during the written statement procedure. In addition, not all potential confounders prespecified in the study protocol were considered ("time since ALL diagnosis", "line of therapy on enrolment date").

Furthermore, there are uncertainties with regard to the rationale for the allocation of patients to the synthetic control arms SCA-1 and SCA-2 on the basis of prior therapy with blinatumomab or inotuzumab ozogamicin, with regard to the specific procedure for allocation and with regard to the specific method of the matching procedure, which could also not be clarified within the framework of the written statement procedure. In particular, it is not clear from the documents submitted whether the methodology prespecified in the study protocol was followed.

With regard to the propensity scores of the patients from the ZUMA-3 study and from the synthetic control arms, it is noticeable that the distributions of the propensity scores before matching differ very clearly between the two groups to be compared. This shows a lack of overlap between the populations and suggests that the likelihood of receiving one of the interventions differs, based on the characteristics of the patients. Overall, it is questionable whether a positivity of the patient groups as a prerequisite for the application of a propensity score procedure is given.

In this context, a relevant selection of the enrolled patients occurred when matching the patients from the ZUMA-3 study with the SCA-1 of the SCHOLAR-3 study. Of the 138 patients of the FAS of SCA-1, only 54 patients were considered for the analysis. A complete characterisation of the enrolled study population was not provided. It is therefore unclear to what extent the patients included in the analysis in the intervention arm are sufficiently comparable with the historical control cohort with regard to relevant patient characteristics.

Furthermore, it is unclear whether the part of the study population included in the analysis sufficiently represents the population in the therapeutic indication.

Overall, the indirect comparison presented shows considerable uncertainties. These are due to the incomprehensible procedure for identifying potential confounders, the uncertainties regarding the positivity of the patient populations used for the indirect comparison as well as the division of the historical control cohort into the synthetic control arms, the uncertainties regarding compliance with the prespecified methodology for the propensity score procedure, as well as the unclear representativeness of the patient population considered in the analysis for the patients covered by the present therapeutic indication. In addition, the resulting effect estimator cannot be meaningfully interpreted due to the highly selected patient population of the indirect comparison and the unclear representativeness for the patients in the present therapeutic indication. The presented indirect comparison of the ZUMA-3 study with the SCHOLAR-3 study is therefore not suitable for the present benefit assessment.

Mortality

Overall survival

The overall survival was defined in the ZUMA-3 study as the time from enrolment in the study until death from any cause. At the time of the data cut-off presented (median duration of observation: 25.1 months), 50.6% of the patients in relation to the FAS had died. The Kaplan-Meier estimate at month 24 was 48.2% and the median overall survival was 23.1 months.

Due to the single-arm study design, a comparative assessment of the data on overall survival is not possible.

Morbidity

Overall complete remission

The endpoint "overall complete response" (OCR) was the primary endpoint of the ZUMA-3 study and included patients who achieved CR, CRi or allogeneic stem cell transplantation. The CR and CRi were collected using the criteria of Cheson et a., 2007. In phase II of the ZUMA-3 study, the assessment was carried out by both the medical investigators and an independent review committee, whereas in phase I, the assessment was carried out exclusively by the medical investigators.

With regard to the FAS, 53.4% (central assessment) and 58.0% (assessment by medical investigators) of the phase II cohort of the ZUMA-3 study achieved an OCR.

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

MRD negativity

The presence of minimal residual disease (MRD) was assessed in the ZUMA-3 study using quantitative PCR (qPCR) or flow cytometric examinations and was defined as $< 10^{-4}$ leukaemic blasts in the bone marrow.

According to central assessment, 59% of patients in the phase II cohort of the ZUMA-3 study had achieved MRD negativity at the time of the data cut-off presented.

Achieving MRD negativity is considered an important prognostic factor in the treatment of ALL. A validation of MRD negativity as a surrogate parameter for overall survival is not available. Therefore, the endpoint of MRD negativity is classified as endpoint of unclear relevance in the assessment and presented additionally. Notwithstanding this, due to the single-arm study design, a comparative assessment of the MRD negativity is not possible.

Duration of response

Duration of response was defined in the ZUMA-3 study as the time between the first CR or CRi until relapse or death from any cause. The assessment was done before initiating subsequent therapy or allogeneic stem cell transplant using the criteria of Cheson et al., 2007. Only the phase II cohort of the ZUMA-3 study was included, as this was the only cohort to be peer-reviewed by an independent review committee.

A total of 47 patients in the phase II cohort of the ZUMA-3 study achieved a CR or CRi. At the time of the data cut-off presented, 40% of these patients had relapsed; 3 (6%) patients had died. The median event-free time was 13.7 months.

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

EQ-5D-VAS

The European Quality of Life 5-Dimension Visual Analogue Scale (EQ-5D-VAS) was to be collected at baseline and at each study visit in phase II of the ZUMA-3 study until month 24. However, the return rate was below 70% as early as day 28. Therefore, the results on the EQ-5D-VAS are not presented.

Quality of life

No data on health-related quality of life were collected in the ZUMA-3 study.

Side effects

In the ZUMA-3 study, one adverse event occurred in all patients who received brexucabtagen autoleucel infusion (Safety Analysis Set (SAS)).

In terms of SAS, 78% of patients experienced a serious adverse event (SAE). Vascular diseases, nervous system disorders and infections and infestations were observed most frequently.

Severe adverse events (CTCAE ≥ grade 3) occurred in 97% of patients overall. Particularly frequent were blood and lymphatic system disorders, altered laboratory parameters (MedDRA system organ class "examinations"), general disorders and administration site conditions as well as metabolism and nutrition disorders.

Relevant adverse events of special interest were cytopenias, neurologic events, cytokine release syndrome and infections.

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

Overall assessment/ conclusion

For the benefit assessment of brexucabtagen autoleucel for the treatment of adults aged 26 years and older with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia, results of the ZUMA-3 study are available for the endpoint categories of mortality, morbidity and adverse events.

Due to the single-arm design of the ZUMA-3 study, a comparative assessment is not possible.

The indirect comparison presented by the pharmaceutical company is subject to considerable uncertainties due to the incomprehensible procedure for the identification of potential confounders, the ambiguities regarding the positivity of the patient populations used for the indirect comparison as well as the division of the historical control cohort into the synthetic control arms, the uncertainties regarding compliance with the prespecified methodology for the propensity score procedure, as well as the unclear representativeness of the patient population considered in the analysis for the patients covered by the present therapeutic indication. In addition, the resulting effect estimator cannot be meaningfully interpreted due to the highly selected patient population of the indirect comparison and the unclear representativeness for the patients in the present therapeutic indication. The presented indirect comparison of the ZUMA-3 study with the SCHOLAR-3 study is therefore not suitable for the present benefit assessment.

As a result, the G-BA classifies the extent of the additional benefit of brexucabtagen autoleucel in the present therapeutic indication as non-quantifiable because the scientific data basis does not allow quantification.

Significance of the evidence

The reliability of data is assessed with a hint, as a comparative assessment is not possible on the basis of the single-arm, uncontrolled ZUMA-3 study and no comparator data suitable for the benefit assessment were submitted.

In the overall assessment, the result is a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient brexucabtagen autoleucel.

Brexucabtagen autoleucel was approved as an orphan drug.

The present therapeutic indication assessed is as follows: Treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

The pharmaceutical company presents results of the single-arm phase I/II ZUMA-3 study for the endpoint categories of mortality, morbidity and adverse events. Due to the single-arm design of the presented study, a comparative assessment is not possible.

The indirect comparison presented by the pharmaceutical company is subject to considerable uncertainties due to the incomprehensible procedure for the identification of potential confounders, the ambiguities regarding the positivity of the patient populations used for the indirect comparison as well as the division of the historical control cohort into the synthetic control arms, the uncertainties regarding compliance with the prespecified methodology for the propensity score procedure, as well as the unclear representativeness of the patient population considered in the analysis for the patients covered by the present therapeutic indication, and is not used for the benefit assessment.

Overall, only data from a single-arm study are available, which do not allow a comparison. The data are therefore not suitable for quantifying the extent of the additional benefit. Data reliability is assessed with a hint because only a single-arm study is available, and a comparative assessment is not possible.

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

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

approx. 81 – 200 patients

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

The resolution is based on the information from IQWiG's dossier assessment (mandate G22-34) and from the resolution on the benefit assessment of inotuzumab ozogamicin (resolution of 18 January 2018). The therapeutic indication of inotuzumab ozogamicin refers to adults with relapsed or refractory CD22-positive B-precursor ALL, whereby adults with Ph-positive relapsed or refractory B-precursor ALL should have prior unsuccessful treatment with at least one tyrosine kinase inhibitor (TKI). However, in the dossier on inotuzumab ozogamicin, the pharmaceutical company did not restrict the target population to patients with CD22-positive ALL and with Ph-positive ALL and previous unsuccessful treatment with at least one TKI. Thus, the size of the target population of the previous procedure is almost the same as the present target population. The only deviation is the lack of restriction to patients 26 years of age and above, which, however, has only a minor effect on the number of patients. The range (123 to

200 patients) given in the procedure for inotuzumab ozogamicin was assessed in the corresponding dossier assessment as largely plausible in terms of magnitude. To account for the uncertainty in the estimates of patient numbers in both procedures, a larger range is set from the lower limit of the present dossier and the upper limit of the dossier on inotuzumab ozogamicin.

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 Tecartus (active ingredient: brexucabtagen autoleucel) at the following publicly accessible link (last access: 8 February 2023):

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

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.
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 brexucabtagen autoleucel 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 1 dose 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 brexucabtagen autoleucel, and to carry the patient emergency card at all times.

Brexucabtagen autoleucel must be used in a qualified treatment facility. The quality assurance measures according to the ATMP Quality Assurance Guideline apply to the use of brexucabtagen-autoleucel in the therapeutic indication B-cell precursor ALL. Annex I CAR-T cells in B-cell neoplasms of the ATMP Quality Assurance Guideline provides further details.

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 March 2023).

The active ingredient brexucabtagen autoleucel is listed on LAUER-TAXE®, but is only dispensed to appropriately qualified inpatient treatment facilities. Accordingly, the active ingredient 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.

Brexucabtagen autoleucel is an autologous cell product produced from the patient's own T cells. Therefore, a leukapheresis is usually necessary to obtain the cell material. Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 of the Medicinal Products Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed.

Treatment period:

Brexucabtagen autoleucel is administered as a single intravenous infusion according to the information provided in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Brexucabtagen autoleucel	Single dose	1	1	1

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[2]

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					
Brexucabtagen autoleucel	1 x 10^6/kg[3]	1 x 10^6/kg	1 single infusion bag	1	1 single infusion bag

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/
[3] For patients over 100 kg, the maximum dose is 1 × 10^8 CAR-positive viable T cells.

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value added tax)	Value added tax (19%)	Costs of the medicinal product
Brexucabtagen autoleucel	1 single infusion bag	€ 282,000	€ 0[4]	€ 282,000

LAUER-TAXE® last revised: 1 March 2023

Costs for additionally required SHI services:

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

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

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Screening for infections with hepatitis B, hepatitis C and HIV

Patients should be tested for hepatitis B, hepatitis C and HIV infection prior to starting treatment with brexucabtagen autoleucel.

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							
Chemotherapy for lymphocyte depletion							
Cyclophosphamide 900 mg/m^2 = 1,710 mg on day 2 prior to infusion							

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

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
Cyclophosphamide	10 PSI	€ 62.76	€ 2.00	€ 4.89	€ 55.87	1	€ 50.28
Fludarabine 25 mg/m² = 47.5 mg on day 4, 3 and 2 prior to Infusion							
Fludarabine 50 mg	2 ml x 25 mg/ml CIS	€ 118.50	€ 2.00	€ 5.09	€ 111.41	3	€ 334.23
Premedication							
Paracetamol 1 x 500 mg - 1 x 1,000 mg	10 TAB x 500 mg 10 TAB x 1000 mg	€ 2.96 € 3.32	€ 0.15 € 0.17	€ 0.13 € 0.14	€ 2.68 € 3.01	1 1	€ 0.27 € 0.30
Diphenhydramine 1 x 12.5 mg - 25 mg	10 TAB 50 mg	€ 2.58	€ 0.11	0.13	€ 2.34	1	€ 0.12
HBV, HCV and HIV screening							
Hepatitis B HBV antibodies (GOP number 32614)	-	-	-	-	€ 5.90	1	€ 5.90
Hepatitis C HCV antibodies (GOP 32618)	-	-	-	-	9.80	1	€ 9.80
HIV HIV-1 and HIV-2 antibodies (GOP 32575)	-	-	-	-	4.45	1	4.45
Abbreviations: CIS = concentrate for the preparation of an infusion solution; PSI = powder for solution for injection; TAB = tablets							

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 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 Brexucabtagen Autoleucel

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

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

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

3. Bureaucratic costs calculation

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

4. Process sequence

On 30 September 2022, the pharmaceutical company submitted a dossier for the benefit assessment of brexucabtagen autoleucel to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 02 January 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 written statements was 23 January 2023.

The oral hearing was held on 6 February 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 March 2023, and the proposed resolution was approved.

At its session on 16 March 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	20 December 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	31 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 February 2023	Conduct of the oral hearing
Working group Section 35a	14 February 2023 28 February 2023	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	7 March 2023	Concluding discussion of the draft resolution
Plenum	16 March 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 March 2023

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

Prof. Hecken