Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V

Autologous anti-CD19-transduced CD3+ cells (mantle cell lymphoma, pretreated patients)

of 5 August 2021

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 for the treatment of a rare disease (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), the additional medical benefit is considered to be proven through the grant of the marketing authorisation 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 evaluation 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 €50 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, subsection 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 marketing authorisation 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 legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient autologous anti-CD19-transduced CD3+ cells in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 4 of the Rules of Procedure of the G-BA (VerfO) is 15 February 2021. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 15 February 2021.

Autologous anti-CD19-transduced CD3+ cells for the treatment of adult patients with relapsed or refractory mantle cell lymphoma is approved as a medicinal product for the treatment of a rare disease 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 German Social Code, Book Five (SGB V), the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence is assessed on the basis of the marketing authorisation studies by the G-BA.

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 17 May 2021 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 G21-08) and the statements made in the written statements and oral hearing process, as well of the addendum 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 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 autologous anti-CD19-transduced CD3+ cells.

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication for autologous anti-CD19-transduced CD3+ cells according (Tecartus) to the product information

Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

Therapeutic indication of the resolution (resolution of 05.08.2021):

see approved therapeutic indication

2.1.2 Extend of the additional benefit and significance of the evidence

Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor

In summary, the additional benefit of autologous anti-CD19-transduced CD3+ cells is assessed as follows:

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

Justification:

For the assessment of the additional benefit, the pharmaceutical company presented data from the single-arm pivotal marketing authorisation study ZUMA-2. In the dossier, the pharmaceutical company also presented an indirect comparison to the ZUMA-2 study based on a meta-analysis of external control studies. Within the framework of the written statement procedure, the pharmaceutical company also submitted an indirect comparison to the ZUMA-2 study on the basis of the external control study SCHOLAR-2.

ZUMA-2 study

ZUMA-2 study is a single-arm Phase II study to evaluate the safety and efficacy of autologous anti-CD19-transduced CD3+ cells (KTE-X19) in adult patients with relapsed or refractory mantle cell lymphoma.

The study included patients with pathologically confirmed mantle cell lymphoma with documented cyclin D1 overexpression or with documented translocation t(11;14) who had received up to five prior therapies, including anthracycline or bendamustine-containing chemotherapy, an anti-CD20 directed monoclonal antibody, and a BTK inhibitor (acalabrutinib or ibrutinib).

Patients were divided into two cohorts. In cohort 1, patients were to be treated with 2 x 10^6 cells per kg body weight and 10 patients treated with axicabtagen ciloleucel were also to be included. For the patients included in cohort 2, a dosage of 0.5 x^{106} cells was planned. Only patients from cohort 1 who were treated with the dose of autologous anti-CD19-transduced CD3+ cells compliant with the marketing authorisation are relevant for the benefit assessment.

The study was divided into several study sections. It started with a screening phase, during which 97 patients were identified. Of these, 74 patients in cohort 1 (hereafter FAS population)

and 17 patients in cohort 2 were subsequently included and underwent leukapheresis. Following this, bridge chemotherapy could be administered at the doctor's discretion. Allowed treatment options for bridge chemotherapy were dexamethasone, ibrutinib, and acalabrutinib. Bridge chemotherapy had to be completed 5 days before the start of the conditioning phase. 38% of the FAS population had received bridge chemotherapy.

After conditioning chemotherapy with fludarabine + cyclophosphamide, the test product was administered in an inpatient hospital setting: 68 patients in cohort 1 received an infusion of autologous anti-CD19-transduced CD3+ cells (KTE-X19). These represent the mITT/safety population. The median time between enrolment / leukapheresis and infusion of autologous anti-CD19-transduced CD3+ cells (KTE-X19) was 27 days. 6 patients discontinued the study before receiving the infusion. Reasons were death (n = 4), withdrawal of consent (n = 1), and other (n = 1).

In the subsequent post-treatment phase, a follow-up up to 3 months after CAR-T cell infusion was planned, a complete recording of all adverse events (AEs)/ serious adverse events (SAEs) was performed. After these 3 months, patients regularly entered the long-term follow-up phase, which lasted up to 15 years. Within these, follow-up focused on survival, disease status, and within the first 24 months, also on specific AE/SAE.

Patients who showed a complete or partial response at month 3 and progressed could be reintroduced to CAR-T cell infusion.

The median age of the FAS population was 65.0 years. 84% of the included patients were male. Patients had an ECOG performance status of 0 (64%) or 1 (36%). Morphologically, 54% of the FAS population had classic mantle cell lymphoma, and 26% had blastoid mantle cell lymphoma. The biological marker Ki-67 had been determined in 49 patients of the FAS population. Of these, 40 patients had a Ki-67 ≥ 30 %. In the FAS population, 18% of patients were at high risk, 41% at intermediate risk, and 39% at low risk, according to the s-MIPI (simplified MCL International Prognostic Index).

18% of the patients in the FAS population had previously received two previous therapies, 46% had received three previous therapies, 20% had received four previous therapies, and 15% had already received five previous therapies. 42 % of the patients had previously been treated with an allogeneic stem cell transplantation.

The study was conducted in 33 centres, mainly in the USA as well as in France, Germany and the Netherlands. The study was launched in May 2016 and is currently ongoing.

In the dossier, the pharmaceutical company had submitted results of the data cut-offs of 24 July 2019 (primary analysis) and 31 December 2019 (update analysis at the request of the EMA). The median follow-up duration from infusion was 10.3 and 14.2 months, respectively, at these data cut-offs.

Within the written statement procedure, the pharmaceutical company submitted results of the data cut-off of 31 December 2020. According to the pharmaceutical company, this is a prespecified update analysis, the data that were not yet available at the time of dossier submission. The median duration of follow-up from infusion at this data cut-off was 25.5 months. Due to the longer follow-up period, the benefit assessment will primarily focus on this data cut-off.

Indirect comparison - meta-analysis

In the dossier, the pharmaceutical company presented an indirect comparison using Matching-Adjusted Indirect Comparison (MAIC) based on a meta-analysis of eight external control studies. These studies are Dreyling et al. 2016, Epperla et al. 2017, Eyre et al. 2019, Jain et al. 2018, Martin et al. 2016, McCulloch et al. 2020, Regny et al. 2019, and Wang et al. 2017. Four studies were used to compare overall survival, two studies were used to compare progression-free survival, and eight studies were used to compare objective response rates.

Only the Dreyling et al. 2016 study is a clinical trial with similar inclusion criteria to the ZUMA-2 study, although baseline characteristics are also not available for the relevant subgroup of the Dreyling study. Overall, the studies in the meta-analysis lack detailed information on inclusion criteria, patient flow, baseline characteristics and operationalisation of endpoints, which would be necessary to demonstrate comparability with the ZUMA-2 study. It can be assumed that, due to the inclusion criteria, a fitter population is represented in the ZUMA-2 study than in the external control studies. Due to lack of data, no adequate adjustment can be made within the MAIC, taking all relevant effect modifiers and prognostic factors into account. Thus, on the basis of the analyses presented, a valid causal effect cannot be estimated. Due to this, the indirect comparison to the meta-analysis is not considered in the benefit assessment.

Indirect comparison - SCHOLAR-2

The pharmaceutical company submitted an indirect comparison to the SCHOLAR-2 study during the written statement procedure. According to the pharmaceutical company, the data of the SCHOLAR-2 study were not available at the time of the dossier submission.

The SCHOLAR-2 study is a retrospective observational study for which individual patient data were extracted from patient records in centres in Denmark, Germany, Spain, Italy, Sweden and the UK. The centres were selected on the basis of a priori defined inclusion criteria. In some cases, data from a registry of the European MCL Network were also included, although it is unclear whether these were collected retrospectively.

The SCHOLAR-2 study included patients with relapsed or refractory mantle cell lymphoma who had received and progressed on BTK therapy or discontinued it due to adverse events during the period July 2012 - July 2018. Furthermore, patients had to have received active therapy again after BTK therapy, and they could not have received CAR-T therapy or other genetically modified therapy. In the SAP for indirect comparison, regarding the comparability to the ZUMA-2 study population that the ECOG status (0-1), no prior allogeneic stem cell transplantation, no more than five prior lines of therapy, and a treatment with anthracycline- or bendamustine-containing chemotherapy and anti-CD20 monoclonal antibodies were defined as important criteria. However, as it was anticipated that its application would lead to a significant reduction in sample size, only ECOG status should be considered as an inclusion/exclusion criterion, and the other factors should be addressed within sensitivity analyses. However, due to a too-small sample of the main analysis, these were not carried out. Against the background of the further inclusion/exclusion criteria, it can be assumed that a non-negligible proportion of the patient population of the SCHOLAR-2 study does not correspond to the population of the ZUMA-2 study.

The pharmaceutical company defined 2 cohorts in the SCHOLAR-2 study for the indirect comparison. Study participants who had an ECOG status of 0 or 1 and did not start their first therapy following BTK inhibitor after 30 June 2019 were included in the initial-line cohort (n =

59). The period-prevalence cohort included study participants who started (not necessarily directly) BTK inhibitor-following therapy between 1 November 2015 and 31 July 2018 (corresponding to the period from the start of the ZUMA-2 study to approximately 12 months before the time of the primary analysis) (n = 40). Since the ZUMA-2 study also did not examine only the therapy line directly following the BTK inhibitor and since there is better concordance on the observation period, the period-prevalence cohort appears to be the most suitable of the defined cohorts for the benefit assessment.

Regarding baseline characteristics, the populations of the ZUMA-2 study and the period-prevalence cohort of SCHOLAR-2 differ particularly concerning the number of previous therapies, gender, disease stage, ECOG status, extranodal disease, bone marrow involvement, and presence of B symptoms. Data on the relevant prognostic factors Ki-67, MIPI and morphology are missing.

Overall, the indirect comparison between the ZUMA-2 and SCHOLAR-2 studies is based on considerable uncertainties, which result in particular from the question of sufficient comparability of the study populations and the small sample size of the SCHOLAR-2 study.

Moreover, taking into account these uncertainties, the comparative effect estimator is not of a magnitude to derive an effect with sufficient confidence. The indirect comparison is therefore not suitable for making statements about the extent of the additional benefit.

Results of the ZUMA-2 study

Mortality

The endpoint overall survival is operationalised in the ZUMA-2 study as time from administration of study medication to death from any cause for analyses on the modified ITT (mITT) population and in the inferential analysis set (IAS) or for the full analysis set (FAS) as the time of enrolment to death. For the benefit assessment, the operationalisation related to the full analysis set is used.

At the 31.12.2020 data cut-off, median survival had not been reached. 32 (43%) of patients were deceased at this time.

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

Morbidity

Progression-free survival (PFS)

Progression-free survival is operationalised as the time from CAR-T cell infusion to death or progression as assessed by an independent radiological review committee according to Lugano criteria and by assessment by medical investigators according to IWG response criteria.

At the 31.12.2020 data cut-off, 27 (45%) of patients had experienced an event based on the inferential analysis set.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" is already assessed via the endpoint "overall survival" as an independent endpoint. The morbidity component "disease progression" is assessed according to IWG response criteria or Lugano criteria and thus not in a symptom-related manner but rather by means of laboratory parametric, imaging, and haematological procedures. Considering the aspects mentioned above, there are different

views within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

Complete response

In the ZUMA-2 study, the endpoint "complete response" represents a subcomponent of the endpoint "best objective response".

The evaluation was based on both the Lugano criteria by an independent radiological review committee and the IWG response criteria by assessment of the medical investigators.

At the 31.12.2020 data cut-off, 46 (62%) of patients had a complete response (assessment by medical investigators).

Due to the single-arm study design, a comparative assessment of response or complete remission rate is not possible.

EQ-5D VAS

Health status was assessed in the ZUMA-2 study using the visual analogue scale of the EuroQoL-5 dimension. The pharmaceutical company submitted responder analyses based on a 10-point deterioration. This did not correspond to a responder threshold of 15% and was not prespecified. It is also unclear whether the calculation of the percentage of subjects with a deterioration of at least 10 points only took into account subjects for whom data were available at both measurement points. Against this background, the data are not considered in the benefit assessment.

In addition, continuous evaluations of the change from baseline are available. At month 3, there was a change of -2.4 compared to baseline.

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

Quality of life

No quality of life data was collected in the ZUMA-2 study.

Side effects

In the ZUMA-2 study, a complete recording of all adverse/serious adverse events was planned from the time of enrolment and thus the performance of leukapheresis until 3 months after the administration of the CAR-T cell product or withdrawal from the post-treatment phase. Subsequently, the recording was selectively limited to specific AEs/SAEs (e.g., neurological AEs/SAEs, hematologic AEs/SAEs, infections, autoimmune diseases, and secondary malignancies) in the period up to 24 months after CAR-T cell infusion or until disease progression. For patients who have not received a CAR-T cell infusion, the recording should be made up to 30 days after the last study-specific treatment.

AEs that occurred after CAR-T cell infusion were evaluated as treatment-emergent adverse events (TEAEs) based on the mITT/safety population.

After infusion of autologous anti-CD19-transduced CD3+ cells (KTE-X19), each patient had experienced at least one adverse event. 67 (99%) of patients had severe AE grade ≥ 3 (according to CTCAE or cytokine release syndrome according to Lee et al. 2014). A serious adverse event occurred in 48 (71%) of patients after CAR-T infusion.

Severe AEs (CTCAE grade ≥ 3) with incidence ≥ 5% and > 1 event were most common in SOC "Blood and lymphatic system disorders". Among the serious AEs with incidence ≥ 5% and > 1 event, "infections and infestations (SOC)" occurred most frequently.

AE of special interest were identified as cytokine release syndrome (91% of patients), neurologic events (63%), cytopenias (thrombocytopenia, neutropenia, anaemia) (96%), infections (53%), and hypogammaglobulinemia (21%).

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

Overall assessment / conclusion

To evaluate the additional benefit of autologous anti-CD19-transduced CD3+ cells for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor, the results of the pivotal single-arm phase II ZUMA-2 study will be used. These include data on mortality, morbidity and side effects. No data on quality of life were assessed.

The indirect comparison with a meta-analysis of eight external studies presented by the pharmaceutical company in the dossier, as well as the indirect comparison with the SCHOLAR-2 study presented in the written statement procedure, are each not suitable for deriving statements on the extent of the additional benefit.

With regard to the meta-analysis, relevant data are missing to establish comparability with the ZUMA-2 study.

The indirect comparison between the ZUMA-2 and SCHOLAR-2 studies is based on considerable uncertainties, which result in particular from the question of sufficient comparability of the study populations and the small sample size of the SCHOLAR-2 study.

Moreover, taking into account these uncertainties, the comparative effect estimator is not of a magnitude to derive an effect with sufficient confidence. The indirect comparison is therefore also not suitable for making statements about the extent of the additional benefit.

In summary, the extent of the available results is classified as non-quantifiable because the scientific data basis does not permit quantification.

Significance of the evidence

The present benefit assessment is based on data from the single-arm ZUMA-2 study. No adequate comparison is available.

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 review, 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 concerns the benefit assessment of the new medicinal product Tecartus® with the active ingredient autologous anti-CD19-transduced CD3+ cells.

Tecartus® was approved under "exceptional circumstances" and as an orphan drug.

Tecartus® is approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

For the benefit assessment, results of the ongoing single-arm study ZUMA-2 on mortality, morbidity and side effects were presented.

With regard to the indirect comparison on the basis of a meta-analysis, relevant data are missing to establish comparability with the ZUMA-2 study.

The indirect comparison between the ZUMA-2 and SCHOLAR-2 studies is based on considerable uncertainties, which result in particular from the question of sufficient comparability of the study populations and the small sample size of the SCHOLAR-2 study.

Moreover, taking into account these uncertainties, the comparative effect estimator is not of a magnitude to derive an effect with sufficient confidence. The indirect comparison is therefore not suitable for making statements about 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 Tecartus® because 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 G-BA bases its resolution on the information from the dossier of the pharmaceutical company. The procedure for determining the number of patients is mathematically comprehensible. However, there are uncertainties that remain even after taking into account the information submitted in the written statement procedure. These concern, in particular the representativeness of the sample of analysed patients with relapsed or refractory mantle cell lymphoma in the third and fourth line (patient groups 1a and 1b) as well as the extrapolation made to the SHI target population.

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: autologous anti-CD19-transduced CD3+ cells) at the following publicly accessible link (last access: 24 June 2021):

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

This medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency (EMA) will assess new information on this medicinal product at least annually and update the product information for healthcare professionals as 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 materials for all healthcare professionals who will prescribe, dispense, and administer autologous anti-CD19-transduced CD3+ cells include 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 complete 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 autologous anti-CD19-transduced CD3+ cells, and to carry the patient emergency card at all times.

The parallel application resolution of 5 August 2021 clarifies that the resolution of 17 September 2020 on quality assurance measures for the use of CAR-T cells in B-cell neoplasms also applies in the context of infusions of autologous anti-CD-19-transduced CD3+ cells in B-cell lymphomas with the diagnosis C83.1 according to ICD-10-GM-2021.

2.4 Treatment costs

The treatment costs are based on the data of the product information and the data of the pharmaceutical company on the dispensing price from module 3 of the dossier.

Tecartus 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 30 or Section 130a SGB V apply. The calculation is based on the sales price of the pharmaceutical company, in deviation from the usually taken into account data of the LAUER-TAXE®.

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

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient	Treatment duration/ treatment (days)	Days of treatment/ patient
Medicinal product to be assessed				
Autologous anti-CD19-transduced CD3+ cells	Single dose	1	1	1

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient	Consumption according to potency
Medicinal product to be assessed					

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient	Consumption according to potency
Autologous anti-CD19-transduced CD3+ cells	10^6 – 2 × 10^6/kg[2]	10^6 – 2 × 10^6/kg	1 single infusion bag	1	1 single infusion bag

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)[3]	Value-added tax	Costs
Autologous anti-CD19-transduced CD3+ cells	1 single infusion bag	€ 360,000.00	€ 0[4]	€ 360,000.00

LAUER-TAXE® last revised: 15 July 2021

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 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 standard expenditure in the course of the treatment are not shown.

Autologous anti-CD19-transduced CD3+ cells are an autologous cell product that is 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 German Medicines Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed.

[2] For patients over 100 kg, the maximum dose is 2 × 10^8 CAR-positive viable T cells.
[3] Information from the pharmaceutical company on the delivery price from module 3 of the dossier.
[4] According to the information provided by the pharmaceutical company, the medicinal product is exempt from value added tax.

The average body measurements were applied for dosages depending on body weight or surface (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)[5].

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceutical 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.

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	Days of treatment/ year	Costs/ patient/ year
Medicinal product to be assessed							
Chemotherapy for lymphocyte depletion							
Cyclophosphamide 500 mg/m² = 950 mg on day 5,4 and 3 before the infusion	1 x 1,000 mg	€ 39.27	€ 1.77	€ 1.56	€ 35.94	3	€ 107.82
Fludarabine 30 mg/m² = 57 mg on day 5,4 and 3 before the infusion	1 x 50 mg	€ 118.26	€ 1.77	€ 5.09	€ 111.40	3	€ 668.40
Premedication							
Paracetamol 1 x 500 - 1,000 mg	10 TAB each 500 mg	€ 1.06[6]	0.05	0.04	€ 0.97	1	€ 0.97

[5] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/
[6] Fixed reimbursement rate

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	Days of treatment/ year	Costs/ patient/ year
Diphenhydramine 1 x 12.5 - 25 mg	10 TAB each 10 mg	€ 2.58[6]	0.13	0.03	€ 2.42	1	€ 2.42

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (contract on price formation for substances and preparation of substances) from 1.10.2009 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 € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional 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 sales price and the maximum surcharge for the preparation and only approximates the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

On 15 February 2021, the pharmaceutical company submitted a dossier for the benefit assessment of autologous anti-CD19-transduced CD3+ cells to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 4 VerfO.

The benefit assessment of the G-BA was published on 17 May 2021 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 7 June 2021.

The oral hearing was held on 21 June 2021.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 9 July 2021.

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 the 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 subcommittee session on 27 July 2021, and the draft resolution was approved.

At its session on 5 August 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 May 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	15 June 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	21 June 2021	Conduct of the oral hearing
Working group Section 35a	29 June 2021 14 July 2021 21 July 2021	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	27 July 2021	Concluding consultation of the draft resolution
Plenum	5 August 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 5 August 2021

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

Prof. Hecken