Justification

Gemeinsamer Bundesausschuss

to 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 Tisagenlecleucel (Reassessment after Expiry: Diffuse Large B-cell Lymphoma)

of 17 September 2020

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1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) 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 SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half 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, numbers 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 during the last twelve 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 medicinal 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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, in the case of 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 provided 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 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 of 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 pharmaceutical company first submitted a dossier for the benefit assessment of the active ingredient tisagenlecleucel (Kymriah®) on 14 September 2018. The resolution of 7 March 2019 passed by the G-BA in these proceedings was limited until 15 March 2020. In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5, Section 1, para 2, No. 7 VerfO, the benefit assessment procedure for the medicinal product (Kymriah®) shall start again on the day the deadline has expired.

For this purpose, on 16 March 2020, the pharmaceutical company submitted the dossier on the benefit assessment to the G-BA in due time (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, No. 5 VerfO).

Tisagenlecleucel for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy is approved as a medicinal product for the treatment of a rare disease 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 sentence 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 are assessed by the G-BA on the basis of the approval studies.

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 July 2020 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 G20-05) 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 evaluated the studies relevant for marketing authorisation 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.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

1 General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

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 adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

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 because the scientific data does not permit quantification

Justification:

The pharmaceutical company presents data on tisagenlecleucel from the JULIET study, a study by the CIBMTR Registry, and a study by the CAR-T-Cell Consortium. The pharmaceutical company also submitted data on the EBMT register within the written statement procedure. In contrast to the pivotal JULIET study, the studies of the CIBMTR Registry, the EBMT Registry, and the CAR-T Cell Consortium are not considered relevant for the benefit assessment. This is partly because the data basis is insufficiently described. Furthermore, the inclusion criteria in the studies sometimes go beyond the therapeutic indication. Furthermore, the observation periods are very short (median observation period of up to 8.42 months in the CIBMTR register, 3.3 months in the EBMT register and 6.2 months in the CAR-T-Cell Consortium study).

The pharmaceutical company presents indirect comparisons to external controls in the form of Technical Reports based on published, aggregated data from the SCHOLAR-1, ZUMA-1, CORAL, Eyre, and PIX301 studies. For the PIX301 RCT, no baseline characteristics were available for the subgroup relevant for the comparison. Sufficient comparability with the JULIET study could therefore not be demonstrated.

With regard to the indirect comparison to the ZUMA-1 study, which represents the pivotal study for axicabtagen ciloleucel, the assessment of the pharmaceutical company cannot be used because of insufficient comparability. Differences between the JULIET study and ZUMA-1 arise with regard to the characteristics of the study population because of differences in the inclusion criteria (inclusion of patients with primary mediastinal B-cell lymphoma (PMBCL)). There are also relevant differences with regard to ECOG status and the proportion of patients who have undergone autologous stem cell transplant. In addition, there are differences in the course of the study, particularly concerning the time between leukapheresis and infusion with the CAR-T cell product as well as the bridge chemotherapy performed during this period.

A comparison with the SCHOLAR-1, CORAL and von Eyre et al. studies was already submitted in the initial assessment. For the CORAL study and the study by Eyre et al., no information beyond the initial assessment was provided. Thus, with regard to the study by Eyre et al., which investigates the treatment of relapsed or refractory DLBCL with pixantrone, the assessment remains that the comparability of patient characteristics to the JULIET study is unclear or non-existent.

With regard to the CORAL study, it was already explained in the initial assessment that the collection of data on third-line chemotherapy, which would be relevant for the benefit assessment in the present therapeutic indication, was only defined retrospectively within a protocol amendment and that the methodology and timing of this retrospective data collection cannot be understood on the basis of the information presented. Eight or nine years had elapsed between the end of the study and the data collection. Because it is unclear how much time had elapsed between the occurrence of the events and their documentation, what efforts

were made in order to achieve data completeness, and how censoring was conducted, there are considerable uncertainties regarding the validity of the data. There are also relevant differences between the JULIET and CORAL studies with regard to patient characteristics and the duration of follow-up (3.71 vs 32.8 months). There is also a difference in the operationalisation of overall survival in both studies; this leads to methodological uncertainties. Against the background of these statements, the studies CORAL and Eyre et al. are not suitable for a valid comparison with the JULIET study.

For the indirect comparison with the SCHOLAR-1 study, the pharmaceutical company presents new data. Sufficient comparability of the study populations cannot be demonstrated. Because of differences in prognostic factors such as age, proportion of patients with DLBCL, and number of previous therapy lines, an unadjusted comparison is not valid. The pharmaceutical company therefore makes an adjustment using MAIC. However, within this adjustment, information on relevant confounders is missing. Furthermore, 20% of the patients included in the JULIET study do not meet the inclusion criteria of the SCHOLAR-1 study. No adjustment can be made in this respect either.

Taking into account the uncertainties regarding the adjustment, the comparative effect estimate presented in the dossier is not of a magnitude that allows an effect to be derived with sufficient certainty. The data are therefore not suitable for making statements about the extent of the additional benefit.

JULIET study

The JULIET pivotal study is a single-arm Phase II study that is being conducted in 27 centres worldwide. The study is still ongoing. In accordance with the requirements defined by the initial evaluation, the pharmaceutical company presents the analyses of a data cut-off of 1 July 2019.

Inclusion in the study took place after the screening phase, during which the leukapheresis was already performed. The screening phase is initially followed by a pre-infusion phase of several weeks, during which patients can receive bridging chemotherapy and lymphocyte-deleting chemotherapy. This should be completed at least 2 to 14 days before the infusion of tisagenlecleucel.

In the JULIET study, there was a median of 115 days (49; 396) between the screening phase. During this time, leukapheresis and the infusion of tisagenlecleucel took place. According to the clinical experts in the written statement procedure, this period is thus significantly longer than that which is available in clinical practice.

The infusion is followed by a primary follow-up phase.

167 patients have been included in the JULIET study. The patients are divided into 2 cohorts depending on the production site (main cohort: US production site n = 147; cohort A: European production site n = 20).

At study enrolment, the median age of the patients included (ITT population) was 58 years. They had an ECOG status of 0 or 1. The majority of patients were in Disease stage IV, and 79.6% of patients had ≥ 2 risk factors in relation to the IPI score. Most patients had received 2 prior therapies. 44.3% of patients in the ITT population had previously been treated with a stem cell transplant.

Of the 167 patients included, 115 (68.9%) received an infusion of tisagenlecleucel. Reasons for discontinuation before the infusion were essentially the occurrence of a fatal event, a doctor's decision, or a tisagenlecleucel manufacturing error. At the time of this data cut-off, 17.4% of the ITT population was still in primary follow-up. The main reason for stopping the primary follow-up was disease progression. After premature termination of the primary follow-up, patients moved on to a secondary follow-up phase. For the present data cut-off, this was 5.4% of the ITT population. 9.0% of the ITT population had entered survival follow-up at that time. At the time of the data cut-off, no patient had entered the long-term observation study, which is based on a separate study protocol.

After infusion with tisagenlecleucel, 7 patients received an allogenic stem cell transplant. 45.2% of patients in the FAS population received further antineoplastic therapy after the infusion.

Mortality

The median observation period for overall survival was 5.9 months for the present data cut-off. In the ITT population, 59.3% of patients had died at this time (median survival of 8.2 months).

In the JULIET study, the Kaplan-Meyer estimator (KM estimator) changes only slightly between Study month 24 and Study month 30.

Morbidity

Overall response

Overall response (CR or PR) is the primary endpoint in the JULIET study. As of protocol version 4, it will be operationalised using the Lugano Classification 2014 based on PET-CT or CT. It was previously operationalised on the basis of the Cheson criteria. It was evaluated on the basis of an Independent Review Committee.

At the time of the data cut-off of 1 July 2019, the overall response rate in the ITT population was 35.9%.

Progression-free survival

In the ITT population of the JULIET study, progression-free survival (PFS) is operationalised as the time from inclusion in the study to progression or relapse or death of the patient, regardless of the underlying cause of death.

At the time of the data cut-off of 1 July 2019, 58.1% of patients had suffered such an event.

Quality of life

FACT-Lym, SF-36

In the JULIET study, the health-related quality of life was assessed using the FACT-Lym and SF-36 questionnaires.

For both questionnaires, the return rates were below 70% during the course of the study. They are therefore considered to be unusable.

Side effects

A complete record of adverse events was made 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, the collection of adverse events was only selective. 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”.

Within the first weeks following the infusion, 85.2% of the ITT population had AE CTCAE grade 3/4. From Study week 9 to Study month 12, 50.0% were affected by such an event.

Serious AE (SAE) occurred in 48.7% of patients in the ITT population from infusion to Study week 8. From Study week 9 to Study month 12, 30.0% of patients had experienced such an event.

Cytokine release syndrome occurred in 57.4% of patients treated with tisagenlecleucel. It represented the most common AE and one of the most common AE of severity 3 or 4 (based on the Penn Grading Scale for Cytokine Release Syndrome (PGS-CRS)).

Overall assessment/conclusion

For the benefit assessment, data on mortality, morbidity, and side effects are available from the single-arm JULIET-1 pivotal study.

There are also data on quality of life. However, these have very low return rates.

The indirect comparison carried out with the SCHOLAR-1 study is considered to be less valid because of the lack of information on relevant confounders and thus insufficient adjustment. There is further uncertainty in the that 20% of the participants in the JULIET study do not meet the inclusion criteria of the SCHOLAR-1 study. No sufficient adjustment is possible in this respect either.

Because of the methodological uncertainties with respect to the adjustment and because the effect estimate is not of such a magnitude that an actual effect can be derived taking into account the uncertainties, the data available cannot be used to derive the extent of the additional benefit.

In summary, the present results are classified as non-quantifiable in their extent because the scientific data basis does not allow quantification.

Significance of the evidence

The JULIET study is single-arm study. A high risk of bias can therefore be assumed. There is no adequate comparison.

There are also uncertainties regarding the follow-up of patients who left the study without an infusion as well as because of a selective survey of adverse events. Uncertainties also arise from the fact that in the JULIET study, leukapheresis and infusion is significantly longer than in clinical care.

In the overall view, there is a hint for a non-quantifiable additional benefit in terms of the significance of the evidence.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of tisagenlecleucel has its legal basis in Section 35a paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V:

Treatment with tisagenlecleucel represents a novel therapeutic approach, the long-term effects of which cannot be fully assessed at present, particularly with regard to a potential cure of the patients. The purpose of the present limitation is to provide further evidence on the long-term effects of tisagenlecleucel on patient-relevant endpoints, which could possibly answer the question of a potential cure of patients, to be included in the benefit assessment.

Conditions of the limitation:

The final results of the JULIET study will be submitted for renewed benefit assessment after 5 years.

With regard to an indirect comparison, it should be examined and explained to what extent an indirect comparison with the 5-year data of the JULIET study can be used, also taking into account any data and information situation that may have developed in the meantime.

In addition, it should be examined and explained to what extent prospective comparative evidence beyond the study justifying the marketing authorisation is available or can be generated for the renewed benefit assessment (e.g. also from observational studies). This could contribute to a relevant further gain of knowledge for the benefit assessment and could, for example, provide information on follow-up therapies administered after the application of tisagenlecleucel.

For this purpose, the G-BA considers a limitation of the resolution until 1 September 2023 to be appropriate.

In accordance with Section 3, paragraph 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of tisagenlecleucel recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of tisagenlecleucel (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO).

The possibility that a benefit assessment for tisagenlecleucel can be carried out at an earlier point in time for other reasons (cf Chapter 5, Section 1 paragraph 2, Nos. 2 to 6 VerfO) remains unaffected by this.

2.1.4 Summary of the assessment

The present assessment is a renewed benefit assessment of the active ingredient tisagenlecleucel because of the expiry of the limitation of the resolution of 7 March 2019.

Kymriah® was approved as an orphan drug.

The current assessment relates to the therapeutic indication claim: “Kymriah is indicated for the treatment of adult patients with relapsed or refractory diffuse large cell B-cell lymphoma (DLBCL) after two or more lines of systemic therapy”.

In accordance with the time limit requirements, the pharmaceutical company submits a data cut-off of 1 July 2019 of the single-arm JULIET study as well as data of further studies on tisagenlecleucel and external historical controls.

Compared with the initial evaluation, the pharmaceutical company presents new data for the indirect comparison with the SCHOLAR-1 study. With regard to the other studies submitted, it is considered that the studies are not suitable for a valid comparison with the JULIET study.

The indirect comparison carried out with the SCHOLAR-1 study is considered to be less valid because of the lack of information on confounders (and thus insufficient adjustment) as well as relevant differences in the inclusion criteria in both studies.

Because of the uncertainties regarding the adjustment and because the effect estimator is not of such a magnitude that an actual effect can be derived taking into account the uncertainties, no statement on the extent of the additional benefit can be made based on results.

Overall, there is a hint of a non-quantifiable additional benefit for tisagenlecleucel for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy because the scientific data base does not allow quantification.

The resolution is limited until 1 September 2023.

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 resolution will be based on the patient numbers from the dossier of the pharmaceutical company.

The sources used by the pharmaceutical company to determine the upper and lower limits for the number of newly diagnosed patients with DLBCL also include patients with other forms of diffuse B-cell lymphoma. Because only one source in the publication used to determine the lower limit is based on a German register, the transferability of the incidence rate to the German healthcare context is also uncertain.

To determine the presence of a relapse or refractoriness to first-line treatment, the pharmaceutical company uses the guidelines of the European Society for Medical Oncology (ESMO). However, the information in these guidelines only pertains to relapses. The percentage rate in the source is not specified as referring to first-line treatment. In addition, the guideline does not specify the methodology for determining the stated figure of 30% and the associated observation period.

In determining the proportion of patients unsuitable for autologous SCT, the pharmaceutical company also includes very old patients (over 80 years of age). However, they are not part of the target population of tisagenlecleucel.

To determine the presence of a relapse of second-line chemotherapy in patients unsuitable for transplantation, the calculated proportion value from the publication used by El Gnaoui et al. does not refer exclusively to second-line therapy. In addition, it is uncertain to what extent the patient population of this study corresponds to the German healthcare context, as this only included patients with CD20-positive DLBCL and 35% of the patients were pre-treated with biological and/or experimental therapies. In addition, the number of patients was low (n = 33), and the median observation period was limited to 28 months. Because of the short observation time, it can be assumed that the percentage share was underestimated, as the possibility cannot be ruled out that other patients would have gone on to relapse after a longer observation period.

In a further calculation step, the pharmaceutical company uses the CORAL study to determine the proportion of patients with refractoriness to second-line therapy. The calculation is performed by inverting the number of patients who went into remission on second-line therapy. In doing so, the company uses the figure for both CR and PR patients. This approach is inadequate because the number of deaths is ignored. The manufacturer relates the figure of 37% arrived at in this way to both patients who are suited for autologous SCT and patients who would not be considered suitable. The assumption that the unit value is transferable to both patient populations is subject to uncertainties. The pharmaceutical company still does not consider patients who show a relapse or refractoriness to a later therapy line; this tends to lead to underestimation.

In order to determine the proportion of patients who do not receive autologous SCT despite remission in second-line therapy and the proportion of patients who suffer a relapse after autologous SCT, the pharmaceutical company makes various assumptions regarding the proportion of patients who do not receive autologous SCT. These are not comprehensible and cannot be justified.

In summary, all calculation steps are based on relevant uncertainties because of the assumptions made and sources used. Overall, an underestimation is to be assumed. This results in particular from the fact that the pharmaceutical company considers only patients who show a refractoriness or relapse after the second line therapy.

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) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 14 August 2020):

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

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material as well as a patient emergency card. The training material for all healthcare

professionals who are to prescribe, deliver, and administer tisagenlecleucel contains instructions for the identification, treatment, and monitoring of cytokine-release syndrome and neurological side effects. It also includes instructions on the thawing of cells, the availability of tocilizumab at the place of treatment, the provision of relevant information to patients, and the full and adequate reporting of side effects.

The patient training programme is designed to educate patients about the risks of cytokine release syndrome and serious neurological side effects as well as the need to report symptoms immediately to the attending physician, stay near the treatment facility for at least four weeks after tisagenlecleucel infusion, and carry their patient emergency card with them at all times.

The resolution of 17 September 2020 on quality assurance measures for the application of CAR-T cells in B-cell neoplasia 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 September 2020). Although tisagenlecleucel is listed in the LAUER-TAXE®, it is only sold to qualified inpatient treatment facilities. The active ingredient is therefore not subject to the Pharmaceutical Price Ordinance, and there are no rebates according to Section 130 or Section 130a SGB V. This differs from the information usually taken into account in the LAUER-TAXE®.

In accordance with the product information, tisagenlecleucel is to be administered as a single intravenous infusion.

Tisagenlecleucel refers to autologous T cells genetically modified ex vivo with a lentiviral vector encoding a chimeric antigen receptor (CAR) directed against CD19. Accordingly, the concentration of CAR-positive viable T cells may vary between patient specific batches. One or more infusion bags contain a total of 1.2×10^6 to 6×10^8 CAR-positive viable T cells.

Treatment duration:

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

Usage and consumption:

In the following, the consumption of infusion bags is presented according to the specifications in the product information. These are administered to the patient in a single infusion depending on the number of cells in each infusion bag. The annual treatment costs of tisagenlecleucel are independent of the actual number of infusion bags used.

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption according to potency
Medicinal product to be assessed					
Tisagenlecleucel					
	0.6–6.0 x 10^8 CAR-positive viable T cells	0.6–6.0 x 10^8 CAR-positive viable T cells	1 or more infusion bags	1	1 or more infusion bags

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (sales price of the pharmaceutical company)	Value added tax	Costs
Medicinal product to be assessed				
Tisagenlecleucel				
	1 or more infusion bags (0.6 to 6 × 10^8 CAR-positive viable T cells)	€ 275,000	€ 0	€ 275,000

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 September 2020

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 costs for the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed 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.

Tisagenlecleucel is an autologous cell product produced from the patient's own T cells. Leukapheresis is therefore regularly necessary to obtain the cell material. Because leukapheresis is part of the manufacture of the medicinal product under Section 4, paragraph 14 AMG, no further costs are incurred in this respect for the medicinal product to be assessed.

According to the product information of tisagenlecleucel, before the administration of the CAR-T cells, the administration of lymphocyte-depleting chemotherapy is recommended provided that the number of white blood cells is not under ≤ 1,000 cells/µl one week before the infusion. For this purpose, a scheme consisting of fludarabine (daily 25 mg/m^2 intravenously over 3 days) and cyclophosphamide (daily 250 mg/m^2 intravenously over 3 days) is preferable. For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis: 1.72 m, average body weight: 77 kg). From this, a body surface of 1.90 m² is calculated (calculation according to Du Bois 1916)[2].

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 September 2020

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Type of service	Cost per package	Cost after deduction of statutory rebates[3,4]	Cost per service	Treatment days per year	Cost per patient/year
Medicinal product to be assessed					
Tisagenlecleucel					
Lymphocyte depletion					
Fludarabine (25 mg/m², i.v.)	€ 115.28 1 × 50 mg	€ 108.42 (€ 1.77, € 5.09)	€ 108.42	3	€ 325.26
Cyclophosphamide (250 mg/m², i.v.)	€ 22.28 1 × 500 mg	€ 19.01 (€ 1.77, € 1.50)	€ 19.01	3	€ 57.03

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating 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 ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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 16 March 2020, 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, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 July 2020 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus

[3] Rebate according to Section 130 SGB V
[4] Rebate according to Section 130a SGB V

initiating the written statement procedure. The deadline for submitting written statements was 22 July 2020.

The oral hearing was held on 10 August 2020.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 8 September 2020, and the proposed resolution was approved.

At its session on 17 September 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	23 June 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	4 August 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 August 2020	Conduct of the oral hearing
Working group Section 35a	18 August 2020 1 September 2020	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 on Medicinal Products	8 September 2020	Concluding discussion of the draft resolution
Plenum	17 September 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 September 2020

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

Prof. Hecken