Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Tisagenlecleucel (reassessment after the deadline (diffuse large B-cell lymphoma, (DLBCL)))

of 15 February 2024

Contents

1. Legal basis

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

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

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

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

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit

assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient tisagenlecleucel (Kymriah) on 31 July 2018. For the resolution of 17 September 2020 made by the G-BA in this procedure, a limitation up to 1 September 2023 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Kymriah recommences when the deadline has expired.

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

Tisagenlecleucel for the treatment of adults 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 rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

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

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 of the additional benefit and the significance of the evidence are assessed on the basis of the approval 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 1 December 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA 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 G23-21) 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 the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4

VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of tisagenlecleucel.

2.1 Additional benefit of the medicinal product

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

Kymriah is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Therapeutic indication of the resolution (resolution of 15.02.2024):

See the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

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

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

Justification:

The pharmaceutical company presents data from the single-arm study JULIET and the observational study A2205B (LTFU) for the new benefit assessment of tisagenlecleucel after expiry of the deadline. In addition, data from the registry study CCTL019B2401 and the study by Bethge et al. 2022 based on the German Registry for Stem Cell Transplantation (GRST) were submitted with the dossier.

JULIET study

The JULIET approval study is a single-arm, phase II study that was conducted in 28 study sites worldwide from 2015 to 2022. In accordance with the time limit requirements, the pharmaceutical company presents the evaluations of the final data cut-off from 22 December 2022. A total of 9 data cut-offs were carried out within the study.

Patients with histologically confirmed DLBCL after two or more lines of chemotherapy, including rituximab and anthracycline, who were unsuitable for or did not consent to autologous stem cell transplantation were enrolled.

Enrolment in the study took place after the screening phase, during which leukapheresis had already been performed. The screening phase was initially followed by a pre-infusion phase lasting several weeks, during which the patients could receive bridging chemotherapy and lymphodepleting chemotherapy was initiated, which should be completed at least 2 to 14 days prior to the infusion of tisagenlecleucel. Administration of tisagenlecleucel infusion was

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

followed by primary follow-up until month 60, disease progression or discontinuation for another reason. Subjects who discontinued primary follow-up or treatment before month 60 were followed up in a secondary follow-up phase for up to 5 years after tisagenlecleucel infusion. For subjects who ended the primary and secondary follow-up prematurely, a survival follow-up followed, which asked about survival status every 3 months until the planned end of study or enrolment in a long-term follow-up study.

The JULIET study enrolled 167 patients and was divided into 2 cohorts depending on the production site (main cohort: US production site n = 147; cohort A: European production site n = 20).

At the time of enrolment in the study, the median age of the enrolled patients (ITT population) was 58 years. They showed an ECOG status of 0 or 1. The majority of patients had stage IV disease and 79.6% of patients had risk factors with regard to the IPI score ≥ 2. Most of the patients had received 2 prior therapies. 44.3% of the patients in the ITT population had previously undergone stem cell transplantation.

Of the 167 patients enrolled, 115 (68.9%) received an infusion of tisagenlecleucel. The main reasons for discontinuation before receiving the infusion were the occurrence of a fatal event, the physician's decision or a tisagenlecleucel production defect.

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

The primary follow-up was completed by 24 patients who received the infusion (20.9%). A total of 57 patients (49.6%) entered the secondary follow-up phase, of which 5 patients completed this phase. A total of 16 patients (13.9%) entered the survival follow-up.

Long-term follow-up (LTFU)

All subjects who withdraw prematurely from the JULIET study or terminate it regularly with the aim of investigating potential long-term damage will automatically be transferred to the ongoing long-term follow-up study LTFU. This survey takes place within the LTFU up to 15 years after tisagenlecleucel infusion. There were no specific exclusion criteria for the study.

4 data cut-offs are currently available for the LTFU study. The data cut-off relevant for the benefit assessment is a data cut-off of an Annual Safety Report from 3 May 2022.

The time of transition of the first patient from the JULIET study is unclear. At the end of the JULIET study, 26 patients who had received an infusion were enrolled in the long-term follow-up (22.6%). Based on the study documents, results are available for 20 patients at the time of the data cut-off from 3 May 2022. At the time of transition, 85% of the subjects were in remission.

<u>On the implementation of conditions for a time limit</u>

According to the justification for the resolution of 17 September 2020, the limitation of the resolution was justified by the fact that further evidence on long-term effects of tisagenlecleucel for patient-relevant endpoints, which could possibly answer the question of a potential cure for patients, could be included in the benefit assessment. For this purpose, the pharmaceutical company should submit the final results of the JULIET study after 5 years

for the new benefit assessment as well as examine and present the possibility of an indirect comparison, taking into account any further development of the data and information basis in the meantime.

In the dossier, the pharmaceutical company presents the final data cut-off of the JULIET study as well as the data cut-off of the long-term follow-up study A2205B.

With regard to possible indirect comparisons, the pharmaceutical company states in the dossier and as part of the written statement procedure that the planned chart reviews could not be carried out due to an incomplete data basis and that indirect comparisons were infeasible.

The time limit requirements are considered to have been implemented.

On the results of the JULIET study:

Mortality

At the final data cut-off of the JULIET study from 22 December 2022, 107 subjects had died. The median survival time of the ITT population in the JULIET study in joint assessment with the LTFU was 8.2 months. The Kaplan-Meier estimator at month 12 is 41.0 and 5 years after enrolment in the study it is 25.5. Due to the high percentage of missing follow-up data from a significant percentage of study participants, the data on overall survival can only be considered valid up to month 60.

An interpretation and comparative assessment of the estimated survival time is not possible due to the missing control group.

Morbidity

Overall response rate (ORR)

The overall response rate was the primary endpoint in the JULIET study and was defined as the percentage of patients with CR or PR from the time of infusion to progression or initiation of new antitumour therapy (including stem cell transplantation), whichever came first.

The assessment was carried out on the basis of an Independent Review Committee and operationalised according to protocol versions 1-3 based on the Cheson criteria, 2007 and protocol version 4 and higher according to IWG criteria (Lugano classification, 2014).

The evaluations are presented additionally.

Overall, 26.9% (assessment by IRC) and 23.4% (assessment by investigators) of study participants in the ITT population achieved a complete response at the final data cut-off of the JULIET study.

Progression-free survival (PFS)

In the ITT population, PFS was defined as the time from enrolment in the study until progression/ relapse or death of the patient, regardless of the underlying cause of death.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The "mortality" endpoint component was assessed as an independent endpoint in the present study via the "overall survival" endpoint. The morbidity component was not assessed on the basis of symptoms according to the operationalisation, but exclusively using imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected by this, as there is no control group, and no statement on the extent of the additional benefit can be derived. The PFS endpoint is presented additionally.

Event-free survival (EFS)

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

The present therapeutic indication generally refers to patients with relapsed or refractory DLBCL after two or more lines of systemic therapy, thus representing a heterogeneous patient population.

Particularly in view of the fact that patients who were eligible for autologous stem cell transplantation were excluded from the study, the number of subjects considered here, for whom an intended curative therapeutic approach can still be assumed, remains unclear.

In the JULIET study, EFS was defined as the time from tisagenlecleucel infusion (for the ITT population, time from enrolment in the study) to progression/ relapse, to initiation of new lymphoma therapy (other than stem cell transplantation), or to patient death, regardless of the underlying cause of death.

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

Quality of life

FACT-Lym, SF-36

Health-related quality of life was assessed in the JULIET study using the FACT-Lym and SF-36 questionnaires.

The return rates for all post-baseline values are < 70% in relation to the population with infusion (does not correspond to the ITT). The data are considered unusable.

Side effects

In the study phase between the start of treatment (start of chemotherapy for lymphocyte depletion) and study month 12, adverse events (AEs) and serious AEs (SAEs) were collected in full, provided that the patients were still in the primary follow-up phase.

In the study phases before the start of therapy, in the primary follow-up and during the secondary follow-up phase, AEs and SAEs are collected selectively. The LTFU study also does not fully collect AEs.

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 an AE of CTCAE grade 3/4. From study week 9 to study month 12, 51% were affected by such an event.

SAEs occurred in 48.7% of patients in the ITT population from infusion to week 8. From week 9 to study month 12, 30% of patients had such an event.

The most common SAE and one of the most common AEs with severity grade 3 or 4 is cytokine release syndrome. It occurred in 57.4% of patients treated with tisagenlecleucel.

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

Overall assessment/ conclusion

The final data on mortality, morbidity, quality of life and side effects as well as data from the long-term follow-up are available from the single-arm, pivotal approval study JULIET. No other data and also no indirect comparison are available.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

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

Significance of the evidence

The data from the single-arm, pivotal study JULIET and the long-term follow-up are available for the benefit assessment.

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

2.1.3 Summary of the assessment

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

Tisagenlecleucel has a marketing authorisation as an orphan drug. This assessment relates to the therapeutic indication: "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.".

The pharmaceutical company has submitted the final data cut-off of the single-arm JULIET studies in accordance with the time limit requirements.

For the benefit assessment, the single-arm data from the JULIET study and the long-term follow-up are taken into account.

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

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

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

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

The resolution is based on the information provided by the pharmaceutical company. As part of the written statement, a recalculation of the patient number range is presented by the pharmaceutical company, which is based on updated information from the Centre for Cancer Registry Data (ZfKD) at the Robert Koch Institute (2018) on DLBCL. The wider range presented by the pharmaceutical company represents a better approximation of the actual target population: 1,046 to 1,903 patients.

In order to allow consistent consideration of the patient numbers taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication, the patient numbers of loncastuximab tesirine (resolution of 2 November 2023) are also used. In this regard, the resolution on the benefit assessment of loncastuximab tesirine (resolution of 2 November 2023) stated a patient number of approx. 680 – 1,200 (patients eligible for CAR-T cell therapy or stem cell transplantation) and approx. 680 – 700 (patients not eligible for CAR-T cell therapy or stem cell transplantation) for correspondingly subdivided patient groups, with a total number of approx. 1,360 – 1,900 patients.

Taking into account the new lower limit for appropriately subdivided patient groups, this results in a patient number of approx. 525 – 1,200 (patients who are eligible for CAR-T cell therapy or stem cell transplantation) and approx. 525 – 700 (patients who are ineligible for CAR-T cell therapy or stem cell transplantation).

For the present benefit assessment of tisagenlecleucel, the relevant patient population eligible for CAR T-cell therapy or stem cell transplantation is used, as tisagenlecleucel itself is a CAR-T cell 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) at the following publicly accessible link (last access: 16 November 2023):

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

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

provision of relevant information to patients, and full and appropriate reporting of side effects.

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

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

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2024).

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

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

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

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

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

Treatment period:

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

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body

measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916).[2]

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tisagenlecleucel					
	0.6 - 6 × 10^8 CAR-positive viable T cells (regardless of the body weight)	0.6 - 6 × 10^8 CAR-positive T cells	1 infusion bag	1	1 infusion bag

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

[2] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), http://www.gbe-bund.de/

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Tisagenlecleucel	1 single infusion bag	€ 239,000.00	0[3]	€ 239,000.00	

LAUER-TAXE® last revised: 15 January 2024

Costs for additionally required SHI services:

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

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

Prophylactic premedication

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

Conditioning chemotherapy for lymphocyte depletion

For tisagenlecleucel, provided the white blood cell count is not below ≤ 1,000 cells/µl one week prior to infusion, a treatment regimen for lymphocyte depletion, consisting of intravenous administration of fludarabine (25 mg/m^2 = 47.75 mg) and cyclophosphamide (250 mg/m^2= 477.5 mg) daily over 3 days starting with the first fludarabine dose, with tisagenlecleucel infusion administered 2 to 14 days after the start of lymphocyte depletion.

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

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

[3] The medicinal product is exempt from value added tax 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
Medicinal product to be assessed							
Tisagenlecleucel							
Conditioning chemotherapy for lymphocyte depletion							
Fludarabine 25 mg/m² = 47.75 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3.0	€ 334.35
Cyclophosphamide 250 mg/m² = 477.50 mg	10 PSI at 200 mg	€ 62.80	€ 2.00	€ 2.85	€ 57.95	3.0	€ 57.95
Screening for HBV, HCV and HIV							
Hepatitis B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1.0	€ 9.80
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.45	1.0	€ 4.45
Abbreviations: CII = concentrate for injection or infusion solution; PSI = powder for the preparation of an infusion solution							

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Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1

SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

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

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

  References:

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

3. Bureaucratic costs calculation

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

4. Process sequence

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

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

The oral hearing was held on 8 January 2024.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 6 February 2024, and the proposed resolution was approved.

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

Chronological course of consultation

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

Berlin, 15 February 2024

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

Prof. Hecken