Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V – Tisagenlecleucel (acute lymphoblastic B-cell leukaemia)

From 7 March 2019

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 condition (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, the additional medical benefit is deemed to be proven through the grant of market 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 comparative 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 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, Nos. 2 and 3 SGB V in conjunction with the 5th Chapter Sections 5 et seq. of the Rules of Procedure of the Federal Joint Committee (G-BA) (VerfO) has not been carried out. Only the extent of the additional benefit must be demonstrated.

However, the restricted benefit assessments for orphan drugs as linked by law to marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical manufacturer must, 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 comparative therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO. In this report, the pharmaceutical manufacturer must also provide evidence of the additional benefit in relation to the appropriate comparative 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; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen). 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 meeting on 15 March 2012 to the effect that, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparative therapy as the basis for the legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided by the G-BA is assessed exclusively on the basis of the approval studies.

Accordingly, at its meeting on 15 March 2012, the Federal Joint Committee amended the mandate given to 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 in such a way that, in the case of orphan drugs, IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparative therapy when the sales volume of the drug 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 shall decide 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 market of the active ingredient Tisagenlecleucel in accordance with Chapter 5, Section 8, paragraph 1, point 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is the 15 September 2018. The pharmaceutical manufacturer has submitted the final dossier to the Federal Joint Committee 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, number 1 VerfO on 14 September 2018.

Tisagenlecleucel for the treatment of relapsed or refractory acute lymphoblastic B-cell leukaemia is authorised as a medicinal product for the treatment of a rare condition under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

In accordance with Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is deemed to be proven through the grant of market authorisation. The extent of the additional benefit is 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 manufacturer in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 17 December 2018 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. An oral hearing was also held.

The G-BA made its resolution on the basis of the dossier of the pharmaceutical manufacturer, the dossier evaluation carried out by the G-BA, the assessment of treatment cost and patient numbers (IQWiG G18-11) prepared by IQWiG, and the statements submitted in the written and oral hearing procedure.

In order to determine the extent of the additional benefit, the Federal Joint Committee has evaluated the studies relevant for 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 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 Federal Joint Committee has arrived at the following assessment:

[1] General methods, Version 5.0 from 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 specialist information

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

2.1.2 Extent of additional benefit of tisagenlecleucel

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

The G-BA classifies the extent of the additional benefit of tisagenlecleucel to be assumed solely from a legal point of view according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V on the basis of the criteria in Section 5, paragraph 7 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable taking into account the severity of the disease and the therapeutic objective in the treatment of the disease.

Grounds:

The results of the pivotal Phase II ELIANA study, the supportive Phase II ENSIGN study, and the Phase I/II PEDICAR study are available to answer the question on the extent of the additional benefit of tisagenlecleucel for the treatment of children, adolescents, and young adults up to 25 years of age with refractory or relapsed (r/r) acute lymphoblastic B-cell leukaemia (B-cell ALL). The pharmaceutical manufacturer also presents indirect comparisons of the study results with historical controls.

<u>PEDICAR study</u>

The PEDICAR supportive study is a single-arm Phase I/II study investigating tisagenlecleucel in patients between 1 and 24 years of age with CD19-positive leukaemia or CD-19-positive lymphoma who are refractory or chemo-resistant. It is unclear whether patients with relapsed disease were in primary or subsequent relapse. It is therefore uncertain as to what extent the patient population fits the approved therapeutic indication of tisagenlecleucel. In addition, it was also possible to administer tisagenlecleucel several times by infusion over a period of 16 days or longer. An effect on the efficacy and safety endpoints as a result of the administration not in compliance with approval cannot be excluded. Because of the uncertainties described above, this study is not used for the benefit assessment.

<u>ELIANA and ENSIGN studies</u>

The pivotal ELIANA study and the supportive ENSIGN study are single-arm, multi-centre Phase II studies to evaluate the efficacy and safety of tisagenlecleucel in children, adolescents, and young adult patients with r/r B-cell ALL.

Because these studies are open-label and non-randomised Phase II studies, a high bias potential is generally assumed for all endpoints.

On the ELIANA study

The study is currently being conducted at 25 study centres in America, Europe, Australia, and Asia. Tisagenlecleucel was administered in a single intravenous infusion. Repeated administration of tisagenlecleucel was not included in the study. After receiving

Tisagenlecleucel infusion, patients were monitored during primary, secondary, or survival follow-up.

The pharmaceutical manufacturer presents a total of four data cut-offs from the ELIANA study (17 August 2016, 25 April 2017, 31 December 2017, and 13 April 2018). These were all not planned a priori. A study report is only available for the first two data cut-offs. The data from the other two data cut-offs are reported as additional analyses in the dossier. According to the pharmaceutical manufacturer's statements at the oral hearing, the data cut-offs were implemented in consultation with the European Medicines Agency. The inclusion of the patients in the ELIANA study was only completed at the time of the last two data cut-offs.

However, for the current data cut-offs of 31 December 2017 and 13 April 2018, important information on the course of study and the conduct of the study is missing. The additional analyses presented did not provide a holistic overview of the course of the study and the flow of patients to the respective data cut-off. In addition, information on the accompanying medication administered (e.g. bridge chemotherapy, chemotherapy for lymphocyte depletion) and the follow-up time of the adverse events as well as an overview of the protocol violations and protocol changes for the respective data cut-off are missing.

With the written opinion, the pharmaceutical manufacturer submits the patient flow before the administration of Tisagenlecleucel for all data cut-offs. However, there is still no information on protocol changes and protocol violations, on the course of the study after administration of tisagenlecleucel, on concomitant medications administered, on the median observation duration of the various follow-up phases of the study, and on the median observation duration of the follow-up for adverse events for the data cut-offs of 31 December 2017 and 13 April 2018.

Following the oral hearing, further information was provided by the pharmaceutical manufacturer on the data cut-off of 13 April 2018 (protocol changes, protocol violations, median duration of follow-up for adverse events). However, information on patient flow after the administration of tisagenlecleucel infusion, on concomitant medications administered, and on median follow-up time after tisagenlecleucel infusion is still missing. After the oral hearing, the pharmaceutical manufacturer did not submit any further documents regarding the data cut-off of 25 April 2017.

Because the course and implementation of the ELIANA study on the data cut-offs of 31 December 2017 and 13 April 2018 cannot be fully traced, these data cut-offs cannot be used for the benefit assessment.

A study report is available for the data cut-off of 25 April 2017. Information on the median duration of the follow-up for adverse events and on the median duration of the secondary follow-up phase is missing. These data are also subject to great uncertainty because the recruitment of patients into the ELIANA study was not yet completed at this time and median follow-up of the infused patients was relatively short (about 10 months).

At the time of the data cut-off of 25 April 2017, 92 patients were enrolled in the study (ITT population (Enrolled Set)). Of the patients included, 17 had discontinued the study before receiving tisagenlecleucel. The reasons for this were death, technical problems in the production of tisagenlecleucel, and the occurrence of adverse events before infusion. A total of 75 patients were treated with tisagenlecleucel. In the ELIANA study, all patients who received a tisagenlecleucel infusion are defined as "Full Analysis Set" (FAS) or Safety Set. In the following, they are referred to as the FAS population. The median time between study inclusion and tisagenlecleucel infusion was 45 days.

After inclusion in the study, a pre-infusion phase of several weeks followed. During this phase, the patients received one or more bridge chemotherapy(s) until completion and infusion of tisagenlecleucel in order to stabilise the disease. This was followed by the lymphocyte depletion phase during which the patients were given lymphocyte-depleting chemotherapy 2 – 14 days before the infusion of tisagenlecleucel. For the FAS population, only summarised information on bridge chemotherapy and subsequent lymphocyte depletion is available. Except for one patient, all patients in the FAS population received bridge chemotherapy and lymphocyte-depleting chemotherapy. The most commonly used antineoplastic agents were cyclophosphamide, fludarabine, methotrexate, cytarabine, and vincristine. In the ITT population, 77 out of 92 patients received bridge chemotherapy.

As of the data cut-off of 25 April 2017, 32 patients in the FAS population were in primary follow-up and 43 patients had stopped prematurely. Of the 43 patients who discontinued primary follow-up, 22 entered secondary follow-up. The main reasons for discontinuing primary follow-up were lack of efficacy (n = 23) and start of a new ALL therapy (n = 13). Death occurred in 5 patients. In the further course of the study, 6 patients discontinued secondary follow-up because of death. At the time of the data cut-off, 14 patients were in survival follow-up. For the ITT population, no data were available on the median follow-up duration overall or for the individual study phases. The total observation period for the FAS population was 9.9 months. The primary follow-up for these patients was 7.2 months (median). For the FAS population, there is also no data available for the secondary follow-up phase.

Antineoplastic therapies after tisagenlecleucel infusion included monoclonal antibodies in 12% of patients (inotuzumab ozogamicine and blinatumomab) and various chemotherapeutic agents. In the study report, the proportion of patients with stem cell transplantation (SCT) after tisagenlecleucel infusion is included in the Patient Data Listings; however, this was not available. In the analysis of the duration of response for seven patients who were in remission, a SCT was described as a reason for censoring. Furthermore, according to the study report, four patients received further CAR-T cell therapy while in remission.

In the ELIANA study, 17 patients dropped out before receiving the tisagenlecleucel infusion. In addition to the large uncertainties of the usable data cut-off of 25 April 2017 resulting from the incomplete recruitment and the relatively short median follow-up time (only about 10 months) of the infused patients, no data on patient characteristics and median follow-up times taking into consideration the ITT population are available for this data cut-off. Although the specialist information on tisagenlecleucel provides details on the patient characteristics of the ITT population, it only covers selective aspects (age, age group, sex, disease status, and previous stem cell transplantation). Thus, amongst others information on the Karnofsky/Lansky performance status, the CNS status, the number of previous therapy lines, and the time between the ALL diagnosis and the first relapse is missing.

Based on the data cut-off as of 25 April 2017, patients in the FAS population were 11 years old (median) and predominantly had a Karnofsky/Lansky performance status of 90–100 % and a CNS status of CNS-1. Most patients were relapsed and received a median of 3 prior therapies. More than half of the patients had a previous SCT. Because there is incomplete information on the patient characteristics of the ITT population, no assessment can be made of the extent to which these differ between infused and non-infused patients. A selection effect between ITT and FAS populations cannot therefore be ruled out.

Moreover, the pharmaceutical manufacturer's dossier does not contain any analyses of overall survival for the ITT population. The pharmaceutical manufacturer only considers patients who have received an infusion with tisagenlecleucel (FAS population). Inherent components of treatment with tisagenlecleucel are the process of leukapheresis, the waiting time until the

product is available, and the frequently associated administration of bridge chemotherapy as well as lymphocyte-depleting chemotherapy. The influence of these components on the treatment of patients with tisagenlecleucel in the clinical care context can only be adequately mapped by considering the ITT population. In the EPAR[2], an evaluation of the overall survival of the ITT population is presented for the data cut-off of 25 April 2017. Only the seven patients who could not receive the infusion with tisagenlecleucel because of death are considered in this evaluation. However, from the safety details of the ELIANA study, it is evident that of the 10 other patients who did not receive infusions for other reasons (e.g. manufacturing problems of tisagenlecleucel or adverse events), an additional seven patients died. Thus, the data listed in the EPAR[2] cannot be used for the benefit assessment. In addition, there are uncertainties because the deaths of the FAS population in this data cut-off do not coincide with the data on patient flow after tisagenlecleucel infusion. According to the pharmaceutical manufacturer, only the primary reason for termination was stated in the patient flow.

With the written statement, the pharmaceutical manufacturer submits evaluations of overall survival for the ITT population based on the data cut-off of the ELIANA study of 13 April 2018 pooled with the data of the ENSIGN study. The comparability of the ELIANA and ENSIGN studies for a pooled analysis is not addressed by the pharmaceutical manufacturer. Because of the different observation times of the studies, no valid conclusions can be drawn based on the pooled overall survival evaluations. In addition, there is no information on censoring and the reasons for censoring.

Following the oral hearing, the pharmaceutical manufacturer provided selective data on patient characteristics of the ITT population for the 13 April 2018 data cut-off (age, gender, ethnicity, origin, weight, and Karnofsky/Lansky performance status). However, this information is not sufficient to assess the comparability between the ITT and FAS populations. Furthermore, the pharmaceutical manufacturer submitted a Kaplan-Meier curve for the overall survival of the ITT population of the ELIANA study. However, the essential details of the underlying data on the number of deaths, censoring, and reasons for censoring were not provided. The pharmaceutical manufacturer did not provide data on patient characteristics and survival time analyses for the ITT population in relation to the data cut-off of 25 April 2017 that could be used for the benefit assessment.

It is objectionable that the pharmaceutical manufacturer did not provide all information deemed necessary for the most recent data cut-off, although both the benefit assessment published on 17 December 2018 and the oral hearing on 29 January 2019 pointed out deficits in the data basis prepared by the pharmaceutical manufacturer. Overall, because of the deficit data provided for the ELIANA study, it is not possible to draw any reliable conclusions on the extent of the additional benefit.

On the ENSIGN study

The study is currently being conducted at nine study centres in the US. The pharmaceutical manufacturer presents a total of two data cut-offs from the ENSIGN study (1 February 2016 and 6 October 2017). These were not planned a priori. A study report is only available for the data cut-off of 1 February 2016. The data of the data cut-off of 6 October 2017 are reported as additional analyses in the dossier. According to the pharmaceutical manufacturer's statements at the oral hearing, the data cut-offs were implemented in consultation with the European Medicines Agency. The inclusion of the patients in the ENSIGN study was only completed at the time of the last data cut-off.

[2] European Public Assessment Report- Kymriah (19 September 2018)

For this study as well, important information on the course and implementation of the study (including patient flow after tisagenlecleucel infusion, concomitant medication administered (e.g. bridge chemotherapy, chemotherapy for lymphocyte depletion), information on follow-up time of adverse events, protocol violations, and protocol changes) is missing for the current data cut-off. With the written statement, the pharmaceutical manufacturer submits information on the patient flow of the ENSIGN study before administration of tisagenlecleucel for the two data cut-offs. However, it does not address the other missing information on the course and implementation of the study.

Following the oral hearing, the pharmaceutical manufacturer did not submit any further information on the ENSIGN study. Because the course and implementation of the ENSIGN study on the data cut-off of 6 October 2017 cannot be fully traced, it cannot be used for the present benefit assessment.

A study report is available for the data cut-off of 1 February 2016. The design of the ENSIGN study largely corresponds to that of the ELIANA study. At the time of the data cut-off of 1 February 2016, 35 patients were enrolled in the study (ITT population (Enrolled Set)). Of these, six patients had discontinued the study before receiving tisagenlecleucel. The reasons for this were death and technical problems in the production of tisagenlecleucel. A total of 29 patients received an infusion of tisagenlecleucel (FAS population). No data are available on the time interval between study inclusion and tisagenlecleucel infusion.

In the pre-infusion phase, which lasted several weeks, all patients in the FAS population received bridge chemotherapy. The most frequently used active ingredients were nitrogen-free analogues, purine analogues, methotrexate, and vinca alkaloids or their derivatives. Lymphocyte-depleting chemotherapy was administered to 27 patients in the FAS population; approximately 90% of patients received fludarabine and cyclophosphamide. Information is not available for the ITT population.

As of the data cut-off of 1 February 2016, six patients in the FAS population were still in the primary follow-up phase, and 19 had discontinued this study phase mainly because of lack of efficacy. Two patients entered the secondary follow-up and were still in this follow-up phase at the time of the data cut-off. There were 13 patients in the follow-up phase for overall survival. In total, the median observation time for the FAS population was 6.4 months. The median duration of the primary follow-up was 5.7 months. Information on the duration of the secondary follow-up phase is not available.

Antineoplastic therapies after tisagenlecleucel infusion included monoclonal antibodies in 24.1 % of patients (among other things, inotuzumab ozogamicine and blinatumomab) and various chemotherapeutic agents. In the study report, the proportion of patients with SCT after tisagenlecleucel infusion is included in the Patient Data Listings; however, this was not available.

The patient characteristics of the FAS population are comparable to those of the ELIANA study. No information on patient characteristics and median follow-up times as well as analyses of overall survival taking into account the ITT population are available for the data cut-off of 1 February 2016. Again, only the primary reason for termination seems to have been documented in the patient flow, thereby resulting in uncertainties because the number of deaths in the overall survival analysis of the FAS population does not correspond to the data on deaths in the patient flow of the study. In the overall view, no reliable conclusions on the extent of the additional benefit can be drawn on the basis of the deficient data available from the ENSIGN study.

Historical comparisons

In order to assess the extent of the additional benefit of tisagenlecleucel for the present therapeutic indication, the pharmaceutical manufacturer presents seven indirect comparisons with historical comparative populations from published studies.

Five of the historical reference populations used do not fit the existing therapeutic indication, or no information is available on the specific ALL diagnosis and/or disease status of the patients. The publication by Miano et al. of 2012 does not indicate the subtype of the ALL (B- or T-cell ALL). In the studies by Locatelli et al. (2009), Jeha et al. (2006), and Stackelberg et al. (2011), the proportion of patients with a B-cell ALL is far below 80% in some cases. There is no separate display of the data for patients with a B-cell ALL. Furthermore, for the publication of Stackelberg et al. (2011), there is no information as to whether the patients were relapsed or refractory. In the publication by Hijiya et al. (2011), 84% of patients have a B-cell ALL. However, the information on the disease status is incomplete because it contains information only on the refractory status of the patients but not on relapse.

The comparative population of Locatelli et al. (2017) is a congress abstract and does not include significant and prognostically relevant patient characteristics such as gender, Karnofsky index, number of prior therapies, presence of extramedullary disease, and time since ALL diagnosis. In addition, information on the course of the study and on the definition of the endpoints is missing. Thus, neither the comparability of the patient populations nor of the endpoints collected can be assessed.

The 2016 study by Stackelberg et al. investigating blinatumomab in paediatric patients with relapsed or refractory ALL is largely within the approved therapeutic indication of tisagenlecleucel. However, there is a lack of further information on patient characteristics such as the Karnofsky index, the presence of an extramedullary disease, the number of prior therapies, and the age at first diagnosis. In addition, the disease status of patients (e.g. refractoriness) appears to be defined differently between the Stackelberg et al. study and the ELIANA and ENSIGN studies. Because of the deficit data provided for the ELIANA and ENSIGN studies, their comparability with the 2016 study by Stackelberg et al. used for the indirect comparison cannot be assessed with sufficient certainty.

In the dossier, the pharmaceutical manufacturer presents a Matched Adjusted Indirect Comparison (MAIC) in which differences between the historical control population data available and the ELIANA and ENSIGN studies are adjusted with regard to some characteristics. However, because of the limited power of a MAIC, not all differences can be considered. In addition, MAICs cannot be adapted for missing information. The pharmaceutical manufacturer adapts the characteristics of the ELIANA and ENSIGN studies to those of the historical comparison population and not vice versa, which would represent the usual methodical procedure. This is not considered adequate. Furthermore, despite the adjustments made by MAIC, there are differences between the adjusted study population and the historical control population. It could therefore not be convincingly demonstrated that a valid comparison between the study population and the historical control population is possible by means of the MAIC.

In addition to the described uncertainties regarding the historical control populations, the overall view of the indirect comparisons presented also reveals considerable uncertainties on the side of the patient population treated with tisagenlecleucel because of the lack of data from the ELIANA and ENSIGN studies. Therefore, no sufficiently valid conclusions can be drawn on the extent of the additional benefit of tisagenlecleucel based on the indirect historical comparisons presented.

Overall assessment

Results on mortality, morbidity, quality of life and side effects from the pivotal single-arm Phase II ELIANA study and the supportive single-arm Phase II ENSIGN study are available for the assessment of the extent of the additional benefit of tisagenlecleucel for the treatment of relapsed or refractory B-cell ALL in children, adolescents, and young adults.

The data presented for the ELIANA and ENSIGN studies are deficient. The current data cut-offs lack elementary information on the conduct of the study and the course of the study. These data cut-offs can therefore not be used for the benefit assessment. The data of the data cut-offs from 25 April 2017 (ELIANA) and 1 February 2016 (ENSIGN) that can be used for the benefit assessment are subject to great uncertainty because of the incomplete recruitment of patients and the short median follow-up period. In addition, for these data cut-offs no patient characteristics and overall survival evaluations are available for the ITT population. Inherent components of treatment with tisagenlecleucel are the process of leukapheresis, the waiting time until the product is available, and the frequently associated administration of bridge chemotherapy as well as lymphocyte-depleting chemotherapy. The influence of these components on the treatment of patients with tisagenlecleucel in the clinical care context can only be adequately mapped by considering the ITT population. Overall, because of the deficient data basis, it is not possible to draw any reliable conclusions on the extent of the additional benefit.

To demonstrate the extent of the additional benefit of tisagenlecleucel, the pharmaceutical manufacturer presents indirect comparisons against various historical controls.

On the basis of the indirect historical comparisons presented, no sufficiently valid conclusions on the extent of the additional benefit of tisagenlecleucel can be derived at present because of the deficit data available from the ELIANA and ENSIGN studies and further uncertainties regarding comparability with the studies used for the indirect comparison.

As a result, the G-BA classifies the extent of additional benefit of tisagenlecleucel as unquantifiable solely from a legal point of view based on the criteria in Section 5, paragraph 7 AM-NutzenV taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. In accordance with Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V, an additional benefit exists but is not quantifiable because the scientific data basis does not permit this.

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 pursuant to Section 35a paragraph 1 SGB V.

On the basis of the data available from the pivotal single-arm Phase II ELIANA study and the supportive single-arm Phase II ENSIGN study, no reliable conclusions can be drawn regarding the extent of the additional benefit of tisagenlecleucel. The present limitation is intended to enable a more meaningful data situation to be included in the benefit assessment also with regard to potentially further findings, in particular on patient-relevant endpoints in treatment with tisagenlecleucel.

Conditions of the limitation

For the renewed benefit assessment, a data cut-off of the ELIANA and ENSIGN studies is to be carried out on 1 July 2019, and a separate report on the study results for this data cut-off is to be submitted for each of the two studies. This report is intended to fully map the data available on the data cut-off for all patient-relevant endpoints, patient characteristics, patient flow, and study outcome for both the FAS and ITT populations.

In addition, it should be examined and explained to what extent evidence beyond the study that justifies the marketing authorisation is available for the reassessment of the additional benefit (e.g. also from observational studies), which could contribute to a relevant further gain of knowledge for the benefit assessment.

With regard to an indirect comparison, it should be examined and explained to what extent any data and information that may have developed in the meantime can be used for an indirect comparison, taking into account the criticisms of the indirect comparison presented in the current assessment.

For this purpose, the Federal Joint Committee considers a limitation of the resolution until 15 March 2020 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 begins again when the deadline has expired. For this purpose, the pharmaceutical manufacturer must submit a dossier to the Federal Joint Committee at the latest on the day of expiry of the deadline 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 – 6 VerfO) remains unaffected by this.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Kymriah® with the new active ingredient tisagenlecleucel. Tisagenlecleucel has been approved as an orphan drug. The present assessment refers to the following therapeutic indication “Kymriah® is indicated for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse”.

The pharmaceutical manufacturer presents the study results of the single-arm Phase II ELIANA and ENSIGN studies and the single-arm Phase I/II PEDICAR study as well as non-adjusted indirect comparisons against various historical control studies.

The PEDICAR study is not included in the benefit assessment because, among other things, a bias of the study results due to the multiple administration of tisagenlecleucel cannot be excluded.

There is deficient data available for the pivotal ELIANA single-arm study and the supportive ENSIGN single-arm study. For the more up-to-date data cut-offs, there is a lack of necessary information on the course and implementation of the studies. These data cut-offs can therefore not be used for the benefit assessment. In the case of the data cut-offs that can be used for the benefit assessment, the data are subject to strong uncertainties because of the very short

median follow-up time and the incomplete recruitment of patients. In addition, for these data cut-offs no patient characteristics and overall survival evaluations are available for the ITT population. Inherent components of treatment with tisagenlecleucel are the process of leukapheresis, the waiting time until the product is available, and the frequently associated administration of bridge chemotherapy as well as lymphocyte-depleting chemotherapy. The influence of these components on the treatment of patients with tisagenlecleucel in the clinical care context can only be adequately mapped by considering the ITT population. Overall, because of the deficient data basis, it is not possible to draw any reliable conclusions on the extent of the additional benefit.

On the basis of the indirect historical comparisons presented, no sufficiently valid conclusions on the extent of the additional benefit of tisagenlecleucel can be derived at present because of the deficit data available from the ELIANA and ENSIGN studies and further uncertainties regarding comparability with the studies used for the indirect comparison.

In the overall view, a non-quantifiable additional benefit is identified from a legal point of view alone.

The resolution shall expire on 15 March 2020.

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

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

The G-BA bases the resolution on the patient numbers stated by the pharmaceutical manufacturer in the dossier.

The share value of 76% determined by the pharmaceutical manufacturer for the cases of an ALL of the B cell line is subject to uncertainties because there is no information in the source of the Leukaemia Competence Network to determine the value. It is also unclear to which age group the value refers.

In determining the presence of relapse or refractory disease, the pharmaceutical manufacturer uses proportions that, to a large extent, do not refer to B-cell ALL but to rather its subtypes (e.g. precursor B-cell ALL or other forms of ALL). The data used are also limited in their timeliness. In some cases, they do not refer to Germany, which places doubt on their transferability to the German health care context. For the determination of refractoriness, the pharmaceutical manufacturer assumes that all patients who show no remission after first-line therapy are refractory. However, it does not take into account potential deaths before the start of a new intervention. In determining the upper limit of relapsed patients, the pharmaceutical manufacturer also includes the proportion of refractory patients from the sources used. The determination of the presence of relapse or refractoriness is therefore subject to uncertainties. In addition, the values determined tend to represent an underestimate because the pharmaceutical manufacturer considers only patients with relapsed or refractory B-cell ALL after first or second line therapy but not after later therapy lines. There is also a potential underestimation because of the limited duration of observation in the studies from which the proportions of patients with relapses were taken. It cannot be ruled out that with prolonged observation, more patients may develop a relapse.

In the overall view, the patient numbers determined are fraught with uncertainties and tend to represent an underestimate.

2.3 Requirements for quality-assured application

A. Regulatory requirements for marketing authorisation

The requirements of the specialist information and the Risk Management Plan (RMP) under the terms of the marketing authorisation must be taken into account. The European Medicines Agency (EMA) provides the contents of the specialist information as well as the conditions or restrictions for the safe and effective use of Kymriah® (active ingredient: Tisagenlecleucel) agreed upon in the context of the market authorisation under the following link (last access: 30 January 2019):

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

According to the requirements of the European Medicines Agency (EMA) regarding additional measures to minimise risk, the pharmaceutical manufacturer must provide training material and 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 four doses of tocilizumab at the site of treatment, the provision of relevant information to patients, and the full and adequate reporting of adverse events.

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.

B. Further requirements for the quality-assured use of tisagenlecleucel in qualified treatment facilities

Against the background of the highly malignant and advanced disease of the patients considered here, the immunosuppressive measures necessary for the administration of tisagenlecleucel as well as the possible very severe CAR-T cell-specific side effects such as CRS[3] and CRES[4], treatment with tisagenlecleucel represents a highly specialised and complex medical service.

The medicinal product must be used at a qualified treatment facility in accordance with the instructions in the summary of product characteristics. Therapy should be started and supervised under the guidance and supervision of healthcare professionals with experience in the treatment of haematological malignancies who are trained in the use of tisagenlecleucel and the management of patients treated with this medicinal product.

An optimal structure and process quality of the treatment facility is required for an optimal benefit-risk assessment for the respective patient and for guaranteeing patient safety by fast and appropriate care, among other things in the event of the occurrence of CAR-T cell-specific side effects such as CRS[3] and CRES[4]. The infrastructure of the treatment facility must also

[3] Cytokine-release syndrome
[4] CAR-T-related encephalopathy syndrome

ensure adequate handling of the final cell product because incorrect handling can relevantly limit the viability of the CAR-T cells and thus the probability of therapeutic success.

Against this background, in order to ensure a reliable and quality-assured supply of the medicinal product, in particular from the point of view of ensuring sufficient patient safety, it is appropriate but also necessary to establish more detailed requirements for the quality-assured use of the medicinal product, in particular with regard to the adequate qualification of a treatment facility.

Taking into account the consistent recommendations of the expert organisations and persons of medical science and practice in the context of the benefit assessment, the Federal Joint Committee assumes that a quality-assured supply of the medicinal product tisagenlecleucel can take place in accordance with the following requirements for quality-assured use. Tisagenlecleucel may only be used at a qualified treatment facility, which must meet at least the following criteria.

1. Requirements for the qualification of the treatment facility

1.1 Extensive experience in the treatment of the respective underlying malignant disease

1.1.1 In adults, documented by the treatment of > 20 cases with this diagnosis (C91.0 according to ICD-10-GM-2018) in the treatment facility within three years and participation in studies of the German Multi-centre Study Group for Adult Acute Lymphoblastic Leukaemia (GMALL) or a comparable multi-centre study group.

Grounds:

The establishment of a minimum quantity in the form of numbers of cases as evidence of sufficient experience to supply the medicinal product is appropriate and justified. The authority to determine minimum quantities is based on Section 35a paragraph 1, sentence 3, number 6 in conjunction with paragraph 3 SGB V. Accordingly, the G-BA should also specify requirements for quality-assured use with the medicinal products with the resolution on the benefit assessment. From the general authority, it can be concluded that from the outset, the legislator did not want to limit the scope of the G-BA to a final catalogue of measures for quality-assured administration. Because the determination of minimum quantities in Section 35a paragraph 1, sentence 3, number 6 in conjunction with paragraph 3 SGB V is not explicitly mentioned as a measure for quality-assured use of medicinal products, it cannot be concluded that it is not covered by the authority. This corresponds to the fact that, according to the case law of the BSG, suitable requirements for minimum quantities (e.g. in the form of minimum patient numbers) can generally also be considered as a quality assurance measure. There is no doubt that minimum quantities can in principle be an instrument of quality assurance (BSG, judgement of 29 November 2017 – B 6 KA 32/16 R, cited by juris, marginal 37 et seq.). Based on the fundamental suitability and social-law recognition of minimum quantities as an instrument of quality assurance, it cannot be concluded from the special regulations on minimum quantities laid down in SGB V as a prerequisite for the provision of certain services by hospitals that minimum quantities in all other areas would be completely excluded as an instrument of quality assurance (cf. BSG, judgement of 29 November 2017 – B 6 KA 32/16 R, cited by juris, marginal 37 et

seq.). In the light of this consideration, the regulations in Section 35a paragraph 1, sentence 3, number 6 in conjunction with paragraph 3 SGB V give the G-BA a sufficiently wide scope for the definition of requirements for the quality-assured use of medicinal products, which also includes the determination of minimum quantities.

R/r B-cell ALL is a rare condition that affects far fewer than 1,000 patients per year in Germany. The treatment of r/r B-cell ALL is a highly specialised and complex service, which requires a special level of practice and experience. For a medically adequate indication, an individual assessment of the available therapy alternatives is necessary because of the lack of comparative study data. Sufficient therapeutic experience in the treatment of B-cell ALL is therefore essential in order to adequately assess the benefit-risk ratio for the use of tisagenlecleucel in multiple pre-treated patients compared with other possible therapy alternatives. Study data for the relationship between treatment volume and mortality specifically for the indication r/r B-cell-ALL are not available. However, for the disease acute myeloid leukaemia (AML), which has a similar complexity with regard to its disease characteristics and the course of therapy, there was a correlation between the amount of treatment and mortality[5]. From these points of view, there is a reasonable probability that a minimum number of cases will lead to considerable quality advantages with respect to the highly specialised and complex medical services available here.

Treatment cases are documented in accordance with the regulations adopted by the G-BA in the field of quality assurance. The application of the regulations adopted by the G-BA in the field of quality assurance remains unaffected in accordance with Item 3 of the requirements for quality-assured administration.

1.1.2 For children and adolescents up to 18 years of age: Fulfilment of the requirements of the Guidelines on Paediatric Oncology of the Federal Joint Committee (Gemeinsamer Bundesausschusses; G-BA).

1.2 Extensive experience in cell therapy

1.2.1 In adults, documented by reporting > 120 allogeneic first transplantations to the German Registry for Stem Cell Transplantation/European Bone Marrow Transplantation Registry (DRST/EBMTR) within the last three years evaluated.

1.2.2 For children and adolescents up to 18 years of age, documented by evidence of allogeneic transplantations in this age group by reporting to DRST/EBMTR within the last three years evaluated.

Grounds:

The use of tisagenlecleucel represents a highly complex treatment approach because of, among other things, the immunosuppressive measures required in most cases and the possible serious side effects. Because of the novelty of the therapy approach, a connection between treatment quantity and treatment quality for tisagenlecleucel and CAR-T cells cannot currently be demonstrated in studies. Therefore, in the present case, the closest therapy concept of allogeneic stem cell transplantation, which has been established for the present indication and treatment

[5] Giri et al. Impact of hospital volume on outcomes of patients undergoing chemotherapy for acute myeloid leukaemia: a matched cohort study. Blood 2015 125:3359–3360

situation, is used. As with CAR-T cells, allogeneic stem cell transplantation requires the administration of high-intensity conditioning chemotherapy, which strongly compromises the patient's immune system. Dealing with severely immunosuppressed patients, including early diagnosis and the treatment of serious infections, is therefore decisive for the rate of serious or fatal complications for both therapeutic approaches. In addition, CAR-T cells as well as allogeneic stem cell transplantation are based on the immunogenic properties of human cells that trigger an immune response. Thus, both therapy approaches can lead to severe immune-mediated complications, which affect multiple organs. In the worst-case scenario, these can lead to death. For the lowest possible mortality and morbidity resulting from acute therapy complications, the rapid and qualified early detection of complications and appropriate intervention are essential. In treatment facilities with sufficient experience in allogeneic stem cell transplantation, it is ensured that personal experience with such complications exists, that the interface to intensive care medicine is adequately defined, that workflows are standardised, and that haemato-oncological expertise also flows into the field of intensive care medicine. There is also the handling of long-term complications and the aftercare of patients. While chronic graft-versus-host-disease is a well-known long-term complication for allogeneic stem cell transplantation, possible long-term sequelae from treatment with tisagenlecleucel are largely unexplained. Potential long-term complications listed by the European Medicines Agency include sustained immunodeficiency or B-cell depletion, secondary tumours, and autoimmune diseases. In treatment facilities with sufficient experience in allogeneic stem cell transplantation or with outpatient specialists cooperating with these treatment facilities, structured aftercare is generally implemented in order to identify long-term consequential damage. For allogeneic stem cell transplantation, study data provide evidence of a causal relationship between treatment volume and mortality as well as the success of therapy (freedom from leukaemia, absence of relapse)[6,7]. Because the common characteristics described between CAR-T cells and allogeneic stem cell transplantation largely determine the quality and risks of the medical service, considerable quality advantages can also be expected for the CAR-T cells through the defined minimum quantities for the performance or detection of allogeneic stem cell transplantation. The present minimum quantities, which were calculated over three years, allow for the compensation of random fluctuations from personnel or organisational aspects. They also prevent a treatment facility from reaching a short-term threshold resulting from a medically unjustified increase in quantities.

Documentation is provided by the reporting of >120 allogeneic first transplantations to the German Registry for Stem Cell Transplantation/European Bone Marrow Transplantation Registry (DRST/EBMTR) within the last three years evaluated. In this respect, it is a special regulation that finally defines the documentation requirements in relation to other regulations of the G-BA (cf Item 3 of the Requirements for Quality Assured Application).

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6 Giebel et al. The impact of centre experience on results of reduced intensity: allogeneic haematopoietic SCT for AML. An analysis from the Acute Leukaemia Working Party of the EBMT. Bone Marrow Transplant. 2013 Feb;48(2):238-42.

7 Loberiza et al. Transplant center characteristics and clinical outcomes after haematopoietic stem cell transplantation: what do we know. Bone Marrow Transplantation volume 31, pages 417–421 (2003)

1.3 Personnel and technical requirements

1.3.1 The medical director and deputy director responsible for treating adults with tisagenlecleucel must be specialists in internal medicine, haematology, and oncology. The medically responsible management or its deputy must have at least two years' professional experience in a treatment centre in which allogeneic stem cell transplantations are carried out in accordance with the criteria set out in Points 1.1 and 1.2 below. If the activity is conducted on a part-time basis, allogeneic stem cell transplantations performed on the ward may be allocated proportionately to full-time work.

1.3.2 For the treatment of children and adolescents up to the age of 18, the management responsible for the treatment with tisagenlecleucel and their deputies must be medical specialists for paediatrics and adolescent medicine with a main focus on paediatric haematology and oncology.

1.3.3 Requirements for the qualification of the nursing service:

1.3.3.1 The management and their representation on the ward for the care of patients treated with tisagenlecleucel are nurses with oncological specialisation or have worked full-time for at least 36 months in a ward with a haematological-oncological specialisation and have participated in the in-house training for the treatment of patients with tisagenlecleucel. If the activity is conducted on a part-time basis, the corresponding working hours may be allocated proportionately to full-time work.

1.3.3.2 Each shift is led by nurses who have worked full-time for at least 12 months in a haematological-oncological ward, have experience in the intensive chemotherapy of leukaemia/lymphoma patients, and have participated in in-house training for the treatment of patients with tisagenlecleucel. If the activity is

conducted on a part-time basis, the corresponding working hours may be allocated proportionately to full-time work.

1.3.4 Sufficient training and documented experience of the medical staff involved (doctors, nurses) in the treatment with cytotoxic and immunosuppressive substances as well as cryopreserved cells must be demonstrated.

2. Infrastructure and organisational requirements

2.1 Establishment of a tumour board:

2.1.1 The indication for treatment with tisagenlecleucel in adults must be presented at an interdisciplinary tumour conference in which at least physicians with the following qualifications participate:

- Internal medicine, haematology, and oncology
- Radiation therapy
- Pathology
- Diagnostic radiology

2.1.2 For children and adolescents up to 18 years of age, specialists in paediatrics and adolescent medicine with a main focus on paediatric haematology and oncology will take part in the tumour conference instead of internal specialists.

2.1.3 The date, participants, and results of the consultation must be documented in writing.

2.2 The responsible pharmacy must be integrated into the treatment facility by binding regulations for the timely fulfilment of statutory requirements.

2.3 The rooms for the treatment of patients with tisagenlecleucel are located in the vicinity of the intensive care unit. The treatment facility must have the necessary equipment to perform at all times endoscopy, including bronchoscopy, invasive ventilation, and renal replacement therapy. Specific SOPs[8] deal with complications of CAR-T cell therapy, including the use and sufficient availability of tocilizumab on site at all times in accordance with the specialist information. There is also a binding and regulated definition of the rapid and unhindered admission of intensive care patients to the intensive care unit.

2.4 There are SOPs[8] for clinical, instrumental, and laboratory chemical monitoring for the early detection of CRS[3] and CRES[4] as well as for the procedure for transferring the patient to the intensive care unit (e.g. resolution-making authority, persons involved).

2.5 Medical care in accordance with specialist standards (internal medicine, haematology, and oncology or paediatric and juvenile medicine with a focus on paediatric haematology and oncology) must be available without interruption for the inpatient care of patients treated with tisagenlecleucel; at least one on-call service must be provided outside working hours. On-call duty means that a specialist of the treatment facility with the corresponding qualification certificates is available to the patient at any time (24 hours a day, seven days a week) within a maximum of 30 minutes.

2.6 When transferring to the intensive care unit, it must be ensured that a visit is carried out daily by a specialist in internal medicine, haematology, and oncology or, in the case of patients up to the age of 18, by a specialist in paediatric and juvenile medicine

[8] Standard Operating Procedure

specialising in paediatric haematology and oncology in the intensive care unit. This physician must have personal experience in treatment with CAR-T cells. The treatment concept for the intensive care unit must be discussed with this physician.

2.7 In addition, the following specialist disciplines must be available at all times; the necessary examinations and treatments should be possible without the need for patient transport (in alphabetical order):

- Ophthalmology
- Gastroenterology (endoscopy of the gastrointestinal tract)
- Vascular surgery
- Otolaryngology
- Cardiology
- Laboratory medicine
- Microbiology (availability within 24 hours sufficient)
- Nephrology (dialysis)
- Neurosurgery
- Neurology (with proof of participation in the in-house training programme)
- Pneumology (bronchoscopy)
- Psychiatry
- Radiology (with CT and MRI)
- Thoracic surgery
- Urology

Outside working hours, at least one on-call standby service must be provided. On-call duty means that a specialist of the treatment facility with the corresponding qualification certificates is available to the patient at any time (24 hours a day, seven days a week) within a maximum of 30 minutes.

2.8 Accommodation in specific rooms for patients in Risk groups 2 or 3 according to the guidelines of the Robert Koch Institute[9] is generally not required. However, it must be ensured that such accommodation is possible at all times.

2.9 Outpatient aftercare

2.9.1 Medical care in accordance with specialist standards (internal medicine, haematology, and oncology or paediatric and juvenile medicine with a focus on paediatric haematology and oncology) must be available without interruption for the outpatient aftercare of patients treated with tisagenlecleucel; at least one on-call service must be provided outside working hours.

2.9.2 The spatial environment must enable the outpatient care of immunosuppressed patients.

2.9.3 The spatial environment must make it possible to examine and treat patients with contagious infections separately. A suitable infrastructure for infusion treatment and the transfusion of blood products must be available.

2.10 Further quality assurance measures

The treatment facility participates in inter-institutional quality assurance and knowledge-generating care measures (registries, quality circles, and analysis of

[9] Recommendation of the Commission for Hospital Hygiene and Infection Prevention at the Robert Koch Institute (RKI). Hygiene requirements for the medical care of immunosuppressed patients. Bundesgesundheitsblatt [Federal Health Bulletin] 2010 53:357–388.

quality indicators) offered nationally or internationally by professional organisations, the pharmaceutical industry, and regulatory authorities.

2.11 Documentation

The documentation is part of the conditions imposed by the European Medicines Agency on pharmaceutical companies. The treatment facility must maintain the personnel and structural requirements for the connection to the planned register modules for CAR-T cells in the German Register for Stem Cell Transplantation (DRST), in the Paediatric Register for Stem Cell Transplantation (PRST), or in the Register of the European Society for Blood and Marrow Transplantation (EBMT) as well as for timely documentation. The following in particular should be documented:

- Prior treatments
- Adverse drug effects
- Type and duration of response
- Follow-up therapies
- Overall survival

3. The findings according to Items 1 and 2 regulate minimum requirements for the quality-assured use of tisagenlecleucel. The validity of other provisions of the G-BA remains unaffected provided that these do not conflict with the minimum requirements.

2.4 Treatment costs

The treatment costs are based on the information in the specialist information, the pharmaceutical manufacturer's information on the selling price from Module 3 of the dossier, and its written statement. Although tisagenlecleucel is listed in Lauer-Taxe® (the recognized price source for all drugs in Germany), it is only sold to qualified inpatient treatment facilities. The active ingredient is therefore not subject to the pharmaceutical price regulation and there are no discounts according to Section 130 or Section 130a SGB V. The calculation is based on the selling price of the pharmaceutical manufacturer. This differs from the information usually taken into account in the Lauer-Taxe®.

As specified in the summary of product characteristics, tisagenlecleucel is administered as a single intravenous infusion.

Tisagenlecleucel concerns 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 to three infusion bags contain a total of 1.2×10^6 to 6×10^8 CAR-positive viable T cells.

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

Usage and consumption:

In the following, the consumption of infusion bags is presented according to the specifications in the specialist 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.

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. To calculate the required cell quantity for patients up to 50 kg, an average body weight of 7.6 kg for children under one year of age was assumed as the lower range[10].

[10] Statistical Office Microcensus 2017: Fragen zur Gesundheit; Körpermaße der Bevölkerung 2017 [Questions about health; body measurements of the 2017 population] [online]. 02/08/2018 [Access: 11/09/2018]. URL: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Dosage	Dose/patient/ treatment days	Consumption according to potency/ treatment day	Treatment days/ Patient/ year	Annual average consumption according to potency
Medicinal product to be assessed					
Tisagenlecleucel					
	Body weight up to 50 kg $0.2–5.0 \times 10^6$ CAR-positive viable T cells/kg	Body weight up to 50 kg 1.52×10^6 to 2.5×10^8 CAR-positive viable T cells	1–3 infusion bags	1	1–3 infusion bags
	Body weight below 50 kg $0.1–2.5 \times 10^8$ CAR-positive viable T cells	Body weight below 50 kg $0.1–2.5 \times 10^8$ CAR-positive viable T cells	1–3 infusion bags	1	1–3 infusion bags

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (Selling price of the manufacturer)[11]	Value added tax	Cost
Medicinal product to be assessed				
Tisagenlecleucel				
	One to three infusion bags (1×10^6 to 6×10^8 CAR-positive viable T cells)	€ 320,000	€ 0[12]	€ 320,000

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 specialist information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

[11] Manufacturer's information on the selling price from module 3 of the dossier.

[12] According to the comments made by the pharmaceutical manufacturer in the statement based on information from the Central Tax Office in Nuremberg in accordance with Section 89 paragraph 2 German Tax Code to the pharmaceutical manufacturer, the supply of tisagenlecleucel (Kymriah®) in accordance with to Art. 132 paragraph 1 lit. d) of the European Value Added Tax Directive or in accordance with Section 4 paragraph 17 lit a) of the Value Added Tax (VAT) Act is qualified as exempt from VAT.

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 usual 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 specialist 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 30 mg/m^2 intravenously over 4 days) and cyclophosphamide (daily 500 mg/m^2 intravenously over 2 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. This results in a range based on the average body surface area of children under 1 year of 0.36 m^2 (average body height: 0.67 m; average body weight: 7.6 kg) and the average body surface area of young adult patients under 25 years of 1.90 m^2 (average body height: 1.75 m; average body weight: 74.7 kg; calculation according to Du Bois 1916)[10].

Type of service	Cost per package	Cost after deduction of statutory discounts[13,14]	Cost per service	Treat-ment days per year	Cost per patient/ year
Medicinal product to be assessed					
Tisagenlecleucel					
Lymphocyte depletion					
Fludarabine (30 mg/m^2, i.v.)	€ 118.20 1 × 50 mg	€ 111.34 (€ 1.77, € 5.09)	€ 111.34–222.68	4	€ 445.36–890.72
Cyclophosphamide (500 mg/m^2, i.v.)	€ 22.80 1 × 500 mg € 29.76 1 × 1000 mg	€ 19.53 (€ 1.77, € 1.50) € 26.95 (€ 1.77, € 1.04)	€ 19.53–26.95	2	€ 39.06–53.90

Pharmaceutical Retail Price (Lauer-Taxe®) as last revised: 15 February 2019

Other SHI services:

The special agreement 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 retail 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: arbitral award to determine the mg prices for parenteral preparations from finished medicinal products in oncology in the Hilfstaxe according to Section 129

13 Rebate according to Section 130 SGB V
14 Rebate according to Section 130a SGB V

paragraph 5c sentences 2 - 5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail 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 production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts 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 Appendix 3 to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"].

3. Bureaucratic costs

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

4. Process sequence

On 14 September 2018, the pharmaceutical manufacturer 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 17 December 2018 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 January 2019.

The oral hearing was held on 29 January 2019.

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 IQWiG also participate in the meetings.

The evaluation of the written statements received and the oral hearing were discussed at the meeting of the subcommittee on 26 February 2019, and the proposed resolution was approved.

At its meeting on 7 March 2019, the plenum adopted a resolution to amend the Pharmaceuticals Guidelines.

Chronological course of consultation

Meeting	Date	Subject of consultation
Subcommittee Medicinal products	11 December 2018	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	15 January 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	29 January 2019	Conduct of the oral hearing
Working group Section 35a	5 February 2019 19 February 2019	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by IQWiG, and the evaluation of the statement procedure
Subcommittee Medicinal products	26 February 2019	Concluding discussion of the proposed resolution
Plenum	7 March 2019	Adoption of a resolution on the amendment of Appendix XII AM-RL

Berlin, 7 March 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof Hecken