Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Tisagenlecleucel (Reassessment after Expiry: B-cell Acute Lymphoblastic Leukaemia)

of 17 September 2020

Contents

1. Legal basis

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

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

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT, exceeds € 50 million during the last twelve calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medicinal benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

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

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (*cf* Section 35a, paragraph 1, sentence 12 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment of the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

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

2. Key points of the resolution

The pharmaceutical company first submitted a dossier for the benefit assessment of the active ingredient tisagenlecleucel (Kymriah®) on 14 September 2018. The resolution of 7 March 2019 passed by the G-BA in these proceedings was limited until 15 March 2020. In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5, Section 1, para 2, No. 7 VerfO, the benefit assessment procedure for the medicinal product (Kymriah®) shall start again on the day the deadline has expired.

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

Tisagenlecleucel for the treatment of: paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed by the G-BA on the basis of the approval studies.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 July 2020 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G20-04) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 - 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tisagenlecleucel.

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

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

2.1 Additional benefit of the medicinal product

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

Kymriah is indicated for the treatment of: Paediatric and young adult patients up to and including 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 the additional benefit and significance of the evidence

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

Hint for a non-quantifiable additional benefit because the scientific data does not permit quantification

Justification:

For the benefit assessment for tisagenlecleucel, the pharmaceutical company submitted data or study documents of the ELIANA, ENSIGN, and PEDICAR studies, a prospective study based on the CIBMTR registry, and the CTL019B2001X study with the dossier. For external controls, the pharmaceutical company presented data from the MT103-205 study as well as a study with clofarabin/toposide/cyclophosphamide.

In accordance with the estimation of the pharmaceutical company, the PEDICAR and CTL019B2001X studies are not considered relevant for the benefit assessment. For the PEDICAR study, this is based on the fact that differences between the study and approval population as well as the dose and number of infusions deviate from the requirements in the product information. No results are presented for the CTL019B2001X study. Deviating from the assessment of the pharmaceutical company, the prospective study based on the CIBMTR register and the study on clofarabin/toposide/cyclophosphamide (CEC) are also not considered relevant for the benefit assessment. For the prospective study based on the CIBMT register, the pharmaceutical company has submitted further data in response to the criticism from the benefit assessment within the statement procedure. The observation period in the CIBMTR register is short (median observation period of up to 9.84 months) These data are thus still not considered relevant for the benefit assessment. The non-relevance of the clofarabin/toposide/cyclophosphamide study is based on the fact that the study population is partly outside the therapeutic indication for tisagenelecleucel and that there is insufficient information on patient characteristics.

<u>ELIANA study</u>

The ELIANA study is a pivotal study. The ELIANA study is a single-arm, multi-centre, uncontrolled Phase II study, which is being conducted at 23 study centres worldwide. The study is still ongoing. The pharmaceutical company has presented the results of a data cut-off of 1 July 2019, in accordance with the requirements defined by the initial resolution.

A study enrolment took place after a screening phase in which the leukapheresis had already been performed. This was followed by a pre-infusion phase of several weeks, during which patients could initially receive one or more bridging chemotherapies. 2 to 14 days before the planned tisagenlecleucel infusion, the lymphocyte-depleting chemotherapy had to be completed. 93.8% of patients in the ITT population had received chemotherapy for bridging and/or lymphocyte depletion.

Between the screening phase, during which the leukapheresis took place, and the infusion of tisagenlecleucel, there was a median of 2.6 months in the ELIANA study and 1.8 months in the ENSIGN study. Accordingly, these periods are longer than those that, according to the clinical experts in the written statement procedure, are available in clinical practice.

97 patients were included in the ELIANA study (ITT population). The median age of the patients was 11 years. The majority of patients had a Karnofsky/Lansky performance status of 100 or 90 and a CNS status of 1. 40.2% of patients had not received a previous stem cell transplant. In the median, the patients had 3 prior therapy lines.

79 of the 97 patients included received a tisagenlecleucel infusion (FAS population). Of the 18 patients who did not receive the tisagenlecleucel infusion, 7 died, 8 others experienced manufacturing problems, and 3 had adverse events prior to the infusion. The infusion of the last patient took place on 28 November 2017.

All patients who had received the tisagenlecleucel infusion entered the primary follow-up phase. At the data cut-off of 1 July 2019, 24.7% of the ITT population was still in the primary follow-up phase. The reasons for discontinuing the primary follow-up phase were lack of efficacy (33%) and the start of a new antineoplastic therapy (15.5%). In the event of premature discontinuation of the primary follow-up phase, patients are transferred to a secondary follow-up phase with longer examination intervals. At the time of this data cut-off, 35.1% of the ITT population had entered this phase and 17.5% of patients had discontinued secondary follow-up. The main reason for this was the occurrence of death event. 14.4% of the patients had moved to the overall survival follow-up and 3.1% to the long-term follow-up, which follows a separate study protocol.

51.9% of the ITT population received further antineoplastic therapy after the tisagenlecleucel infusion. No evaluable data are available on the proportion of patients who subsequently received an allogenic stem cell transplant.

ENSIGN study

The ENSIGN study is a single-arm, multi-centre and uncontrolled Phase II study, which was originally submitted as a supportive study as part of the approval process.

In accordance with the time limit requirements, for the ENSIGN study, the pharmaceutical company should also conduct a data cut-off on 1 July 2019 and submit a separate report on the study results with all data available for the ITT and FAS populations.

Because the study had already been completed before 1 July 2019, the pharmaceutical company presented the results of the final data cut-off of 24 May 2019.

As in the ENSIGN study, the study enrolment took place after a screening phase in which the leukapheresis had already been performed. This was also followed by a pre-infusion phase of several weeks, during which patients could initially receive one or more bridge chemotherapies. 2 to 14 days before the planned tisagenlecleucel infusion, the lymphocyte-depleting chemotherapy had to be completed. 97.3% of patients in the ITT population had received chemotherapy for bridging and/or lymphocyte depletion.

The ENSIGN study includes 75 patients. The median age of these patients was 13.0 years. Also in this study, the majority of patients had a Karnofsky/Lansky performance status of 100 or 90 and a CNS status of 1. 57.3% of patients had not received a stem cell transplant. In the median, they had 3 prior therapy lines.

Of the 75 patients included, 64 (85.3%) were able to be given the tisagenlecleucel infusion. In the remaining 11 patients, a death event occurred previously, or there was no product release. The infusion of the last patient took place on 5 December 2017.

85.3% of patients received a tisagenlecleucel infusion and thus entered primary follow-up. 22.7% of patients had moved to secondary follow-up, 26.7% to overall survival follow-up, and 41.3% to long-term follow-up. In this study, too, the main reason for terminating the primary follow-up was a lack of efficacy. The main reason for terminating the secondary observation was the occurrence of a death event.

46.9% of patients received another antineoplastic therapy following the tisagenlecleucel infusion. Also in this study, there are no evaluable data available on the proportion of patients who subsequently received an allogeneic stem cell transplant.

Historical comparisons

The pharmaceutical company presents indirect comparisons with historical populations from two different studies. One is the MT103-205 study and the other a study on clofarabin/toposide/cyclophosphamide (Hijiya et al. 2011). With regard to the study of Hijiya 2011, it can be stated that the study population is partly outside the therapeutic indication, the population is restricted with regard to previous stem cell transplantation, and that relevant characteristics of the study population are not available. Accordingly, this study is not considered relevant for the benefit assessment. The MT103-205 study, on the other hand, is considered as relevant or a possible control for the benefit assessment. In this respect, the pharmaceutical company refers to the publications Gore et al. 2018 and von Stackelberg et al. 2016 as well as the benefit assessment on blinatumumomab (resolution of 15 May 2019).

The MT103-205 study is a single-arm, multi-centre, uncontrolled Phase I/II study. Included were patients < 18 years of age with refractory/relapsed B precursor cell ALL who had a second or later bone marrow recurrence, any bone marrow relapse after allogeneic stem cell transplantation, or were refractory to other treatments.

In the dossier, the pharmaceutical company presents two different analytical strategies for the purpose of indirect comparison. Based on the results of the publications of von Stackelberg et al. 2016 and the benefit assessment for blinatumomab, a matched-adjusted indirect comparison (MAIC) was carried out. Furthermore, an indirect comparison based on individual patient data was carried out based on information from the publication Gore et al.

According to the documents of the pharmaceutical company, there are differences between the populations of the ENSIGN and ELIANA studies and the MT103-205 study in terms of age, sex, geographical region, refractory status or refractoriness compared with the last previous therapy, the number of relapses, the length of remission after initial response, the proportion of patients with blasts ≥ 50%, the proportion of patients with previous stem cell therapy, and the proportion of patients with extramedullary disease. An adjustment is considered necessary.

Within the MAIC, an adjustment was made only for the number of relapses and the performance of a previous SCT. According to the pharmaceutical company, a comprehensive adjustment was not possible because of the limited sample size.

Because of this lack of adjustment and the fact that a MAIC without a bridge comparator does not lead to reliable results, the results of the MAIC cannot be used to derive the extent of the additional benefit.

For the indirect comparison, a time-to-event analysis was carried out on the basis of the individual data of the publication Gore et al. taking into consideration the available confounders. However, because in the Gore et al. study, information was available only for a limited number of confounders and prognostic factors, no comprehensive adjustment was made. Thus, no adjustment was made for remission duration after initial response, the proportion of patients with blasts ≥ 50%, and the proportion of patients with extramedullary disease. Differences continued to exist with regard to age and the inclusion of patients with Ph+-ALL. These criticisms were partially addressed during the written statement procedure. However, it cannot be ruled out that the comparison may be distorted by other unrecorded or unknown confounders.

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

Mortality

Overall survival

In relation to the ITT population, 45.6% of patients in the ELIANA study had died at the time of the data cut-off of 1 July 2019 and 48% of patients in the ENSIGN study at the time of the data

cut-off of 24 May 2019. In the ELIANA study, median overall survival was not achieved for this data cut-off (median observation period of 24.9 months). In the ENSIGN study, the median overall survival at this time (median observation period of 13.6 months) was 25.9 months.

In the ELIANA study, the Kaplan-Meyer estimator (KM estimator) changes only slightly between Study month 18 and Study month 24.

In the absence of comparative data, it is not possible to draw conclusions about the extent of the additional benefit based on these results.

Morbidity

Response (CR(CRi)

In the ELIANA and ENSIGN studies, the response was operationalised on the basis of defined criteria; these are based on the criteria of Cheson et al. 2003 as well as the NCCN guideline (Version 1.2013). The assessment was carried out by an independent review committee. A response was considered as such only if it had lasted for at least 28 days. Response is the primary endpoint in both studies; a period of 3 months was defined in the ELIANA study and 6 months in the ENSIGN study.

After 6 months, 60% of the ITT population showed a response in the ENSIGN study and 68% in the ELIANA study.

Relapse-free survival (RFS)

In both studies, relapse-free survival was defined as the time from reaching remission/response until relapse or death of any cause.

The occurrence of a relapse was assessed by an independent review committee based on defined criteria.

For these data cut-offs 36.4% of patients in the ELIANA study and 28.9% in the ENSIGN study who had a response experienced events that were considered as a relapse.

Health status

In the ELIANA study, health status was assessed using the visual analogue scale of the EQ-5D VAS.

The survey was conducted only in patients who were at least 8 years old. Even when only this patient group was considered, the return rate to the questionnaires was only over 70% at the time of screening. The data are therefore not classified as usable.

Quality of life

Health-related quality of life

In the ELIANA study, quality of life was surveyed using the PedsQL questionnaire. The questionnaire comprises four multi-dimensional scales (physical function, emotional function, social function, and academic functioning) and three summary scores (total score, Physical Health Summary Score, and Psychosocial Health Summary Score).

The survey was conducted only in patients who were at least 8 years old. Even when considering only this patient group, the return rate to the questionnaires was always below 70% throughout the study. The data are therefore not classified as usable.

Side effects

A complete record of adverse events was made from the start of chemotherapy for lymphocyte depletion until Study month 12 of the primary follow-up phase. Both after Study month 12 and at the transition to the secondary follow-up phase, the collection of adverse events was only selective. The follow-up period of the first 12 months was divided into the phases “Chemotherapy for lymphocyte depletion”, “Infusion until Study week 8”, and “Study week 9 to Study month 12”.

Within the first weeks following the infusion, 83.5% of patients in the ELIANA study and 84.4% of patients in the ENSIGN study experienced an adverse event with CTCAE grade 3/4. In the following period until Study month 12, almost 50% of the patients in both trials experienced such an event. Serious AEs occurred in 68.4% and 71.9% of the patients in the studies in the period from infusion up to and including Study week 8. In the period from Study week 9 to Study month 12, 31.1% and 37.5% of patients experienced a serious AE.

77.2% of patients in the ELIANA study and 78.1% of patients in the ENSIGN study suffered the AE of special interest “cytokine release syndrome”.

Overall assessment/conclusion

Data on mortality, morbidity, and side effects are available from the ELIANA pivotal study and the ENSIGN supportive study.

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

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

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

Significance of the evidence

The ELIANA and ENSIGN studies are single-arm uncontrolled studies. A high risk of bias can therefore be assumed. There is no adequate comparison.

There are also uncertainties with regard to the large proportion of censorship because of, among other things, lost to follow-up and the sometimes short median observation period in

relation to overall survival as well as with regard to adverse events because of a selective survey.

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

2.1.3 Limitation of the period of validity of the resolution

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

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

Conditions of the limitation:

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

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

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

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

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

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

2.1.4 Summary of the assessment

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

Kymriah® was approved as an orphan drug.

The present assessment refers to the following therapeutic indication “Kymriah® is indicated for the treatment of paediatric and young adult patients up to and including 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 company presents new data cut-offs of the ELIANA and ENSIGN studies as well as data from other studies on tisagenlecleucel and external historical controls in accordance with the time limit requirements.

For the benefit assessment, the ELIANA and ENSIGN pivotal studies will be considered. In terms of historical controls, the MT103-205 study on blinatumomab is considered relevant.

The pharmaceutical company presents a matched-adjusted indirect comparison (MAIC) as well as an indirect comparison based on individual patient data between the ELIANA and ENSIGN studies as well as the external control MT103-205.

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

Overall, there is a hint of a non-quantifiable additional benefit for tisagenlecleucel for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia that is refractory or in relapse because the scientific data basis does not allow quantification.

The resolution is limited until 1 September 2023.

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

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

The calculation procedure of the pharmaceutical company in the present dossier largely corresponds to the procedure described in the dossier on the initial resolution. However, there is a difference in that in the present dossier, the incidence of lymphatic leukaemia is used as the basis for calculation instead of acute lymphatic leukaemia. It is considered more appropriate to use figures based on the incidence of acute lymphatic leukaemia. Accordingly, the resolution is based on the patient numbers from the initial resolution of 7 March 2019.

In this respect, it should be noted that the share value of 76% used by the pharmaceutical company for the cases of an ALL of the B-cell line is subject to uncertainties because there is no information available in the underlying 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 refractoriness, the pharmaceutical company 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 healthcare context. For the determination of refractoriness, the pharmaceutical company assumes that all patients who show no remission after first-line treatment 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 company 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 company 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 a quality-assured application

The requirements in the product information and the Risk Management Plan (RMP) under the terms of the marketing authorisation are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) 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 marketing authorisation at the following publicly accessible link (last access: 12 August 2020):

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

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material as well as a patient emergency card. The training material for all healthcare professionals who are to prescribe, deliver, and administer tisagenlecleucel contains instructions for the identification, treatment, and monitoring of cytokine-release syndrome and neurological side effects. It also includes instructions on the thawing of cells, the availability of tocilizumab at the place of treatment, the provision of relevant information to patients, and the full and adequate reporting of side effects.

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

The resolution of 17 September 2020 on quality assurance measures for the application of CAR-T cells in B-cell neoplasia provides further details.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 September 2020). Although tisagenlecleucel is listed in the LAUER-TAXE®, it is only sold to qualified inpatient treatment facilities. The active ingredient is therefore not subject to the Pharmaceutical Price Ordinance, and there are no rebates according to Section 130 or Section 130a SGB V. This differs from the information usually taken into account in the LAUER-TAXE®.

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

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

Treatment duration:

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

Tisagenlecleucel	Single dose	1	1	1

Usage and consumption:

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

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[2].

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

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

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption according to potency
	10^8 CAR-positive viable T cells				

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (sales price of the pharmaceutical company)	Value added tax	Costs
Medicinal product to be assessed				
Tisagenlecleucel	1 or several infusion bags (1.2×10^6 to 6×10^8 CAR-positive viable T cells)	€ 275,000	€ 0	€ 275,000

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

Costs for additionally required SHI services:

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

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

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

According to the product information of tisagenlecleucel, before the administration of the CAR-T cells, the administration of lymphocyte-depleting chemotherapy is recommended provided that the number of white blood cells is not under ≤ 1,000 cells/µl one week before the infusion. For this purpose, a scheme consisting of fludarabine (daily 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).[2]

Type of service	Cost per package	Cost after deduction of statutory rebates[3,4]	Cost per service	Treatment days per year	Cost per patient/year
Medicinal product to be assessed					
Tisagenlecleucel					
Lymphocyte depletion					
Fludarabine (30 mg/m^2, i.v.)	€ 115.28 1 × 50 mg	€ 108.42 (€ 1.77, € 5.09)	€ 108.42 – 216.84	4	€ 433.68 – 867.36
Cyclophosphamide (500 mg/m^2, i.v.)	€ 22.28 1 × 500 mg € 29.07 1 × 1000 mg	€ 19.01 (€ 1.77, € 1.50) € 26.26 (€ 1.77, € 1.04)	€ 19.01 – 26.26	2	€ 38.02 – 52.52

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

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.
According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe”] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

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

3. Bureaucratic costs

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

4. Process sequence

On 16 March 2020, the pharmaceutical company submitted a dossier for the benefit assessment of tisagenlecleucel to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 July 2020 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 July 2020.

The oral hearing was held on 10 August 2020.

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

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

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	23 June 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	4 August 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 August 2020	Conduct of the oral hearing
Working group Section 35a	18 August 2020 1 September 2020	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	8 September 2020	Concluding discussion of the draft resolution
Plenum	17 September 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 September 2020

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

Prof. Hecken