Gemeinsamer Bundesausschuss

# Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Ciltacabtagene autoleucel (relapsing/ refractory multiple myeloma, after at least 3 prior therapies)

of 17 August 2023

**Contents**

## 1. Legal basis

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

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

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

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

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

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

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

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

## 2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was 15 February 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA for the first placing on the (German) market of the active ingredient ciltacabtagene autoleucel. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 14 February 2023.

Ciltacabtagene autoleucel indicated for the treatment of relapsing/ refractory multiple myeloma is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs.

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

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

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 May 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G23-04) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation 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 ciltacabtagene autoleucel.

## 2.1 Additional benefit of the medicinal product

### 2.1.1 Approved therapeutic indication of Ciltacabtagene autoleucel (Carvykti) according to the product information

Carvykti is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

**Therapeutic indication of the resolution (resolution of 3 August 2023):**

see the approved therapeutic indication

### 2.1.2 Extent of the additional benefit and significance of the evidence

Adults with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

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

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

Justification:

In the dossier, the pharmaceutical company submitted data from the single-arm, open-label phase Ib/II CARTITUDE-1 study for the assessment of the additional benefit of ciltacabtagene autoleucel in the therapeutic indication of relapsed and refractory multiple myeloma (≥ 3 prior therapies). In addition, the pharmaceutical company presented an indirect comparison without a bridge comparator with data from the prospective, non-interventional LocoMMotion study in the dossier.

As part of the written statement procedure, the pharmaceutical company submitted data from the randomised, controlled phase III CARTITUDE-4 study comparing ciltacabtagene autoleucel versus pomalidomide in combination with bortezomib and dexamethasone (PVd) or daratumumab in combination with pomalidomide and dexamethasone (DPd) as supplementary data in order to use them to eliminate potential uncertainties regarding the structural equality of the patient characteristics of the indirect comparison.

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Furthermore, supplementary analyses for the indirect comparison presented in the dossier were submitted as part of the written statement procedure. These included the final data cut-off of the LocoMMotion study, new inclusion criteria for the analysis population of the LocoMMotion study, and a pooled analysis of the CARTITUDE-1 and CARTITUDE-4 studies compared to the LocoMMotion study.

*CARTITUDE-1 study*

The single-arm, open-label CARTITUDE-1 study to evaluate the efficacy and safety of ciltacabtagene autoleucel in subjects with relapsed or refractory multiple myeloma who have previously received at least three lines of therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD-38 antibody, was conducted between June 2018 and August 2022 at a total of 17 study sites in the US and 4 study sites in Japan.

A total of 35 subjects were enrolled in phase Ib and 118 subjects in phase II. Included subjects had to have received at least three prior myeloma therapies, which included an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, or be double refractory to an immunomodulator and a proteasome inhibitor. Furthermore, disease progression had to have occurred during or within the last 12 months after the last line of therapy or within the last 6 months in the case of refractoriness or non-response to the previous line of therapy. The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of the enrolled subjects was 0 or 1.

The study consisted of a screening phase (approximately 28 days before leukapheresis), a pretreatment phase in which bridge therapy was allowed, a treatment phase which included conditioning chemotherapy and ciltacabtagene autoleucel infusion, and long-term follow-up.

The primary endpoint of the CARTITUDE-1 study was overall response rate, assessed by an independent review committee based on International Myeloma Working Group (IMWG) criteria. Other endpoints included overall survival, minimal residual disease (MRD) negativity rate, progression-free survival (PFS), adverse events and quality of life (for phase II study participants).

In the dossier, the prespecified data cut-off of 11.01.2022 was presented.

*LocoMMotion study*

The LocoMMotion study is a prospective, non-interventional study that was used by the pharmaceutical company for an indirect comparison of ciltacabtagene autoleucel with standard therapy in everyday care. The LocoMMotion study was conducted from August 2019 to November 2022 at 72 study sites in Europe and 14 study sites in the USA.

The inclusion criteria of the LocoMMotion study were similar to those of the CARTITUDE-1 study. Initially, 248 subjects were enrolled in the study, of whom only those were included in the analysis population who corresponded to the therapeutic indication of ciltacabtagene autoleucel and who had received one of the therapy options defined by the pharmaceutical company. This resulted in a number of N = 174 for the external comparison population.

The comparator therapy included in the analysis population comprised a total of 47 different treatment regimens. Carfilzomib in combination with dexamethasone (n = 26); cyclophosphamide in combination with pomalidomide and dexamethasone (n = 24) and pomalidomide in combination with dexamethasone (n = 19) were used most frequently.

*CARTITUDE-4 study*

The ongoing CARTITUDE-4 study is an open-label, randomised study comparing ciltacabtagene autoleucel versus PVd or DPd in patients with multiple myeloma who have previously received 1-3 prior therapies, including an immunomodulatory agent and a proteasome inhibitor.

Patients with more than three prior therapies were not enrolled. For the benefit assessment of ciltacabtagene autoleucel, the pharmaceutical company submitted evaluations for a sub-population comprising adults with three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody. Those included in the analysis population show disease progression during the last line of therapy.

In the intervention arm of the CARTITUDE-4 study, patients regularly received one cycle of bridge therapy (usually PVd or DPd, depending on previous myeloma therapy) after leukapheresis, followed by conditioning therapy for lymphocyte depletion and ciltacabtagene autoleucel infusion.

The primary endpoint of the CARTITUDE-4 study is progression-free survival (PFS). Other endpoints include overall survival, complete response as well as stringent complete response, overall response, MRD negativity as well as adverse events and quality of life.

The CARTITUDE-4 study has been conducted since June 2020 at a total of 88 study sites in Europe, Asia, USA and Australia. The planned end of the study is after the occurrence of approximately 250 deaths within the total population.

A total of 419 people were enrolled in the study (ITT population). Stratification was done according to the number of previous lines of therapy (1 vs 2 or 3). Evaluations of the first, prespecified data cut-off from 1 November 2022 were presented.

The evaluation submitted by the pharmaceutical company for a sub-population (subjects with three prior therapies), includes 49 persons (intervention arm: N = 20; control arm: N = 29) and thus, only 11.7% of the total population of the CARTITUDE-4 study.

This evaluation of the CARTITUDE-4 study was additionally submitted by the pharmaceutical company within the scope of the written statement procedure in order to eliminate potential uncertainties regarding the structural equality of the patient characteristics of the indirect comparison. No statements on the extent of the additional benefit are derived by the pharmaceutical company on the basis of these data alone.

Notwithstanding this, relevant information is missing from the submitted documents, including the documentation of the course of the study and the patient flow. There are no reasons for discontinuation of therapy or non-administration of the ciltacabtagene autoleucel infusion.

The results of this evaluation for a sub-population of the CARTITUDE-4 study are therefore not used as the basis for the present assessment of the extent of additional benefit. Nevertheless, the data are presented additionally.

*Indirect comparison between CARTITUDE-1 and LocoMMotion*

In the dossier for the benefit assessment of ciltacabtagene autoleucel, the pharmaceutical company presented an indirect comparison without a bridge comparator based on data from the single-arm, open-label phase Ib/II CARTITUDE-1 study and the prospective, non-interventional LocoMMotion study. As part of the written statement procedure, supplementary analyses were submitted taking into account the final data cut-off of the LocoMMotion study and the randomised controlled trial CARTITUDE-4.

In the dossier, evaluations were presented according to different adjustment methods (unadjusted, propensity score-based weighting for Average Treatment Effect on Treated (ATT)

and Average Treatment Effect (ATE) approach, propensity score matching) with a main adjustment set and a sensitivity adjustment set.

The inclusion and exclusion criteria for the comparison cohort of the LocoMMotion study were defined according to the therapeutic indication of ciltacabtagene autoleucel, resulting in a number of N = 174 patients for the external comparison population.

However, with regard to the analyses presented in the dossier, it is unclear to what extent the entire LocoMMotion cohort would have been suitable for CAR T-cell therapy or inclusion in the CARTITUDE-1 study. General condition and suitability for CAR-T cell therapy were only shown in the comparison cohort using the inclusion criterion ECOG-PS, whereas in the CARTITUDE-1 study, it was selected from a variety of exclusion criteria for them. The inclusion and exclusion criteria of the LocoMMotion study thus do not fully represent the medical suitability and selection mechanisms for CAR T-cell therapy. The existence of a selection bias can therefore not be ruled out. Based on the statistical analyses, a positivity of the two study populations cannot be shown on the basis of the available data.

The limitations mentioned above could not be completely eliminated by the data submitted as part of the written statement procedure.

However, according to the assessment by the clinical experts, the patient collectives of the CARTITUDE-1 and LocoMMotion studies are comparable and the patients of the LocoMMotion study are basically suitable for CAR-T cell therapy.

Irrespective of this assessment by the clinical experts, positivity cannot be considered given on the basis of the statistical models with defined criteria.

In order to achieve the necessary structural equality, it is necessary to take all relevant confounders into account as adjustment variables when carrying out an indirect comparison without a bridge comparator. The pharmaceutical company's selection of the confounders was systematic and is assessed as appropriate. A total of 12 confounders were identified for the main analysis.

In terms of the analyses, there is a high number of missing values in some key baseline characteristics and potential confounders in the LocoMMotion cohort, as well as in different collection times and methods of the baseline characteristics in the two studies. Information on the patient characteristics of the overlapping naive patient population was not provided in the written statement procedure. The overlap on the basis of the available data is small; a conclusive assessment cannot be made.

Overall, there is not sufficient balance between the study populations.

This is particularly evident in the weighted analyses (including ATE analysis). Pseudopopulations were created with the aim of eliminating potential confounding. For the ATE analysis, 126 and 136 subjects (out of 124 from the CARTITUDE-1 study and 110 from the LocoMMotion study, respectively) were included in the main adjustment set as a result of weighting. On the basis of the documents presented, it cannot be conclusively assessed to what extent the pseudopopulations generated differ from the total population and whether the results for the pseudopopulations can be transferred to the total population. In terms of balance, there are inadequate SMDs (standardised mean difference) for 4 of the 12 confounders used. The balance is therefore considered insufficient.

In addition, based on the analyses carried out (e.g. trimming), there are high case number losses.

Overall, the lack of balance and the high case number losses mean that the weighted analyses submitted by the pharmaceutical company cannot be interpreted meaningfully.

Propensity score matching also leads to strong patient selection in both cohorts. Forty-eight subjects each from the CARTITUDE-1 study (38.7%) and the LocoMMotion study (43.6%) were included in the main adjustment set. On the basis of the documents presented, it cannot be conclusively assessed to what extent the sub-population studied differs from the total population and whether the results for the sub-population can be transferred to the total population.

In view of the aforementioned reasons, the submitted indirect comparison between the CARTITUDE-1 and LocoMMotion studies is assessed overall to the effect that it does not form a sufficient data basis to the extent required for this purpose in order to be able to derive plausible statements on the quantification of the additional benefit. The indirect comparison is therefore not used for the present benefit assessment.

*Pooled analysis of the CARTITUDE-1, CARTITUDE-4 and LocoMMotion studies*

Furthermore, a pooled analysis of the CARTITUDE-1, CARTITUDE-4 and LocoMMotion studies, based on the individually collected patient data, was submitted as part of the written statement procedure.

Here, the CARTITUDE-1 study and the intervention arm of the CARTITUDE-4 study were treated as if they were from a clinical study. Significant differences in study design, such as different methods and times of collecting disease-specific baseline characteristics and different specifications for bridge therapy, as well as different follow-up times were not taken into account.

The heterogeneity between studies can lead to a relevant risk of bias if not taken into account.

The pooled analysis of the CARTITUDE-1, CARTITUDE-4 and LocoMMotion studies is considered unsuitable for the benefit assessment.

*On the endpoints of the CARTITUDE-1 study:*

Mortality

The endpoint of overall survival in the CARTITUDE-1 study was defined as the time from infusion with ciltacabtagene autoleucel till death of the patient. At the time of the data cut-off presented for the benefit assessment (duration of observation: 28.6 months), a total of 39 subjects (31.5%) had died. Overall survival at month 24 was 73.9%.

Due to the single-arm study design, a comparative assessment of the data on overall survival is not possible.

Morbidity

*Progression-free survival (PFS)*

PFS is defined in the CARTITUDE-1 study as the time from infusion with ciltacabtagene autoleucel to the first documented disease progression according to International Myeloma Working Group (IMWG) criteria, based on laboratory parameters as well as haematology and imaging, or death from any cause, whichever occurs first. Patients who have no documented disease progression and are alive will be censored at the time of the last disease assessment before receiving subsequent anti-myeloma therapy.

The median PFS in the CARTITUDE-1 study was 27.4 months.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The “Mortality” endpoint component is already assessed via the “overall survival” secondary endpoint as an independent endpoint. The morbidity component "disease progression" was assessed according to IMWG criteria and thus, not in a symptom-related manner but by means of laboratory parametric, imaging, and haematological procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

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

*Overall response rate*

Overall response rate is the primary endpoint in the CARTITUDE-1 study and is defined as achieving a partial or better response as assessed by an independent review committee using the IMWG criteria.

The overall response rate in the CARTITUDE-1 study was 83.1% in the ITT population.

The overall response rate is presented additionally as a primary endpoint of the study.

Due to the single-arm study design, a comparative assessment of the data on overall response rate is not possible.

*EQ-5D-VAS*

General health status was assessed for patients in phase II of the CARTITUDE-1 study (PRO population) using the European Quality of Life - 5 Dimensions visual analogue scale (EQ-5D-VAS).

The return rate of the EQ-5D-VAS was already less than 70% after day 100, so that the submitted responder analyses are considered unsuitable for the benefit assessment.

*Symptom scales of the EORTC-QLQ-C30*

The symptoms of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea were assessed using the symptom scales of the EORTC-QLQ-C30 in patients of the PRO population of the CARTITUDE-1 study.

Results are available on progression scores of the EORTC QLQ-C30 symptom scales and responder analyses on time to first improvement/ deterioration for a responder threshold of 10 points. There are no data available on the period between screening and infusion. This makes the time interval between the initial screening and day 7 (day 7 after infusion) unclear.

The return rate of the EORTC QLQ-C30 symptom scales was already less than 70% after day 100, so that the submitted responder analyses are considered unsuitable for the benefit assessment.

Regardless of this, a comparative assessment of the data on the EQ-5D-VAS and the symptom scales of the EORTC QLQ-C30 is not possible due to the single-arm study design.

Quality of life

*Quality of life scales of the EORTC QLQ-C30*

Quality of life was assessed using the EORTC-QLQ-C30 in patients of the PRO population of the CARTITUDE-1 study.

Results are available on EQ-5D-VAS progression scores and responder analyses on time to first improvement/ deterioration for a responder threshold of 10 points. There are no data available on the period between screening and infusion. This makes the time interval between the initial screening and day 7 (day 7 after infusion) unclear.

The return rate of the EORTC QLQ-C30 was already less than 70% after day 100, so that the submitted responder analyses are considered unsuitable for the benefit assessment.

*Individual items of the EORTC QLQ-MY20*

Quality of life was assessed in the PRO population of the CARTITUDE-1 study using four individual items from two scales of the QLQ-MY20. The individual items "restlessness and agitation" of the symptom scale "side effects of treatment" as well as "thoughts about the disease", "concern about dying" and "concern about the health status in the future" of the future perspectives scale were collected.

On the basis of the documents submitted, it is unclear to what extent the evaluation of individual items is validated or whether the individual items are only validated within the entire questionnaire. Studies on the validity of the individual items outside the questionnaire as well as a justification for the selection of the individual items were not provided.

Nevertheless, a comparative assessment of the data on the EORTC QLQ-C30 and -MY20 is not possible due to the single-arm study design.

Side effects

In the CARTITUDE-1 study, 99.2% of patients in the ITT population experienced at least one adverse event (AE).

Severe AEs occurred in 95.2% and serious adverse events in 62.9% of patients. Blood and lymphatic system disorders (93.5%), especially neutropenias (87.1%) and anaemias (70.2%) were observed most frequently. Relevant adverse events of special interest were cytopenias and infections.

A comparative assessment of side effects is not possible due to the single-arm study design.

Overall assessment

Data from the label-enabling, single-arm, multicentre phase Ib/II CARTITUDE-1 study are available for the benefit assessment. Furthermore, the pharmaceutical company presents an indirect comparison between the CARTITUDE-1 study and the prospective, non-interventional LocoMMotion study without a bridge comparator. In the written statement procedure, it also presents pooled analyses of the CARTITUDE-1 and CARTITUDE-4 studies in comparison with the LocoMMotion study, as well as supplementary data from the randomised, controlled phase III CARTITUDE-4 study.

With regard to the presented analyses of the indirect comparison (weighted analyses, PS matching), there are considerable uncertainties regarding the comparability of the study populations, especially with regard to balance and high case number losses. Overall, the submitted indirect comparison is assessed to the effect that it does not form a sufficient data

basis to the extent required for this purpose in order to be able to derive plausible statements on the quantification of the additional benefit.

The pooled analysis of the CARTITUDE-1, CARTITUDE-4 and LocoMMotion studies is considered unsuitable for the benefit assessment due to heterogeneity.

The data on the sub-population of the CARTITUDE-4 study are not used as a basis for the present assessment, but are presented additionally.

The pharmaceutical company submitted data on mortality, morbidity, quality of life and side effects for the CARTITUDE-1 study. However, these data do not allow for a comparative assessment due to the single-arm study design.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The benefit assessment is based on data from the single-arm phase Ib/II CARTITUDE-1 study.

Since only single-arm data are available and a comparative assessment is not possible, the reliability of data is assessed with a hint.

The overall assessment gives a hint for 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 ciltacabtagene autoleucel finds 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 the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The European Medicines Agency (EMA) commissioned the pharmaceutical company to submit the final results of the phase III CARTITUDE-4 study on the basis of the conditional marketing authorisation for the present therapeutic indication. The deadline mentioned in the conditions was December 2026.

Since more clinical data which could be relevant for the benefit assessment of the medicinal product are expected, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of ciltacabtagene autoleucel. The limitation enables inclusion of the expected results from the CARTITUDE-4 study - to be submitted to the EMA - in the benefit assessment of the medicinal product in accordance with Section 35a SGB V.

For this purpose, the G-BA considers a limitation for the resolution until 1 July 2026 to be appropriate.

*Conditions of the limitation:*

For the new benefit assessment after expiry of the deadline, the significant results from the CARTITUDE-4 study on all patient-relevant endpoints used for the evidence of an additional benefit are to be presented in the dossier for the present therapeutic indication.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3, No. 7 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 1, paragraph 2, No. 6 Rules of Procedure (VerfO), the procedure for the benefit assessment of the medicinal product ciltacabtagene autoleucel 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 ciltacabtagene autoleucel (Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, No. 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product ciltacabtagene autoleucel can be carried out at an earlier point in time due to other reasons (cf. Chapter 5 Section 1, paragraph 2, Nos. 2 to 4 VerfO) remains unaffected hereof.

### 2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Carvykti with the active ingredient ciltacabtagene autoleucel.

Ciltacabtagene autoleucel was approved as an orphan drug under special conditions for the treatment of adults with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

For the benefit assessment, data from the single-arm phase Ib/II CARTITUDE-1 study and an indirect comparison between the CARTITUDE-1 study and the prospective, non-interventional LocoMMotion study without a bridge comparator are available. In the written statement procedure, the pharmaceutical company also submits pooled analyses of the CARTITUDE-1 and CARTITUDE-4 studies in comparison with the LocoMMotion study, as well as supplementary data from the randomised, controlled phase III CARTITUDE-4 study.

With regard to the presented analyses of the indirect comparison (weighted analyses, PS matching), there are considerable uncertainties regarding the comparability of the study populations, especially with regard to balance and high case number losses. Overall, the submitted indirect comparison is assessed to the effect that it does not form a sufficient data basis to the extent required for this purpose in order to be able to derive plausible statements on the quantification of the additional benefit.

The pooled analysis of the CARTITUDE-1, CARTITUDE-4 and LocoMMotion studies is considered unsuitable for the benefit assessment due to heterogeneity.

The data on the sub-population of the CARTITUDE-4 study are not used as a basis for the present assessment, but are presented additionally.

The pharmaceutical company submitted data on mortality, morbidity, quality of life and side effects for the CARTITUDE-1 study. However, these data do not allow for a comparative assessment due to the single-arm study design.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

The period of validity of the resolution is limited to 1 July 2026.

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

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

The resolution is based on the information from the dossier of the pharmaceutical company. These are based on the number of patients in the SHI target population determined in the benefit assessment procedure of idecabtagene vicleucel (resolution of 16 June 2022).

Since the target population is the same, the pharmaceutical company's approach is considered plausible. Based on the previously determined number of patients, the pharmaceutical company calculates the number of patients for 2023, assuming a mean annual rate of increase in the 5-year prevalence of 0.80%, which is based on data from the Centre for Cancer Registry Data of the Robert Koch Institute.

In addition to the uncertainties of the estimate from the benefit assessment on idecabtagene vicleucel, there are also uncertainties with regard to the applied increase factor. Nevertheless, the information provided is the best possible estimate based on the data currently available.

This results in about 1,210 to 1,310 subjects in the SHI target population.

## 2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Carvykti (active ingredient: ciltacabtagene autoleucel) at the following publicly accessible link (last access: 23 June 2023):

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

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient emergency card. Training material for all healthcare professionals who will prescribe, dispense, and administer ciltacabtagene autoleucel includes instructions for identifying, treating, and monitoring cytokine release syndrome and neurological side effects. It also includes instructions on the cell thawing process, availability of 1 dose of tocilizumab at the point of treatment, provision of relevant information to patients, and full and appropriate reporting of side effects.

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

Ciltacabtagene autoleucel must be used in a qualified treatment facility.

The quality assurance measures according to the ATMP Quality Assurance Guideline apply to the use of ATMP ciltacabtagene autoleucel in the therapeutic indication of multiple myeloma.

Annex I – CAR-T cells in B-cell neoplasms of the ATMP Quality Assurance Guideline provides further details.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

## 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 August 2023).

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

Ciltacabtagene autoleucel is administered as a single intravenous infusion according to the specifications in the product information.

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

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 | | | | |
| Ciltacabtagene autoleucel | Single dose | 1 | 1 | 1 |

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).[2]

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

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Ciltacabtagene autoleucel | ≤ 100 kg: 0.5 – 1 x $10^6$ viable CAR+ T cells per kg | 0.5 – 1 x $10^6$/kg | 1 single infusion bag | 1 | 1 single infusion bag |
| | > 100 kg: 0.5 – 1 x $10^8$ viable CAR+ T cells | 0.5 – 1 x $10^8$/kg | | | |

Costs:

**Costs of the medicinal products:**

| Designation of the therapy | Packaging size | Costs (purchase price clinic pack plus value added tax) | Value added tax (19%) | Costs of the medicinal product |
|---|---|---|---|---|
| Ciltacabtagene autoleucel | 1 single infusion bag | € 420,000 | € 0 [3] | € 420,000 |

LAUER-TAXE® last revised: 1 August 2023

Costs for additionally required SHI services:

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

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

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing

[3] The medicinal product is exempt from value added tax at the applied LAUER-TAXE® last revised.

price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

*Prior chemotherapy for lymphocyte depletion*

The treatment regimen for lymphocyte depletion, consisting of intravenous administration of cyclophosphamide[2] (300 mg/m$^2$ = 570 mg) and fludarabine[2] (30 mg/m$^2$ = 57 mg), is given daily for 3 days, with infusion of ciltacabtagene autoleucel 5 to 7 days after the start of lymphocyte depletion.

*Premedication*

For premedication, an antipyretic (paracetamol, 650-1000 mg, peroral or intravenous) and an antihistamine (diphenhydramine, 25-50 mg, peroral or intravenous) are administered 30-60 min before the start of treatment.

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

The presence of HBV, HCV and HIV infection must be tested prior to initiation of treatment with ciltacabtagene autoleucel.

| Designation of the therapy | Packaging size | Costs (pharmacy sales price) | Rebate Section 130 SGB V | Rebate Section 130a SGB V | Costs after deduction of statutory rebates | Treatment days/ year | Costs/ patient/ year |
|---|---|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | | | |
| *Chemotherapy for lymphocyte depletion* | | | | | | | |
| Cyclophosphamide[2] 300 mg/m$^2$ (= 570 mg) 1 x daily intravenously for 3 days | | | | | | | |
| Cyclophosphamide | 6 PSI | € 84.41 | € 2.00 | € 9.25 | € 73.16 | 3 | € 73.16 |
| Fludarabine[2] 30 mg/m$^2$ (= 57 mg) 1 x daily intravenously for 3 days | | | | | | | |
| Fludarabine<br>2 ml each 25 mg/ml | 1 CIS | € 118.50 | € 2.00 | € 5.09 | € 111.41 | 3 | € 668.46 |
| *Premedication* | | | | | | | |
| Paracetamol<br>1 x 500 mg - 1 x 1,000 mg | 10 TAB x 500 mg | € 2.96 | € 0.22 | € 0.19 | € 2.55 | 1 | € 0.25 |
| | 10 TAB x 1,000 mg | € 3.32 | € 0.19 | € 0.16 | € 2.97 | 1 | € 0.30 |

| Designation of the therapy | Packaging size | Costs (pharmacy sales price) | Rebate Section 130 SGB V | Rebate Section 130a SGB V | Costs after deduction of statutory rebates | Treatment days/ year | Costs/ patient/ year |
|---|---|---|---|---|---|---|---|
| Diphenhydramine<br>1 x 25 mg - 1 x 50 mg | 20 CTA x 25 mg<br>20 TAB x 50 mg | € 3.70<br>€ 4.38 | € 0.15<br>€ 0.17 | € 0.13<br>€ 0.14 | € 3.42<br>€ 4.07 | 1<br>1 | € 0.34<br>€ 0.41 |
| *Screening for HBV, HCV and HIV* | | | | | | | |
| Hepatitis B virus (HBV) antibodies<br>(GOP number 32614) | - | | | | € 5.90 | 1 | € 5.90 |
| Hepatitis C virus (HCV) antibodies<br>(GOP number 32618) | - | | | | € 9.80 | 1 | € 9.80 |
| Human immunodeficiency virus (HIV)-1 and HIV-2 antibodies<br>(GOP number 32575) | - | | | | € 4.45 | 1 | € 4.45 |
| Abbreviations: CIS = concentrate for the preparation of an infusion solution; PSI = powder for solution for injection; TAB = tablets, CTA = coated tablets | | | | | | | |

Other SHI services:

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

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

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

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

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

## 3. Bureaucratic costs calculation

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

## 4. Process sequence

On 14 February 2023, the pharmaceutical company submitted a dossier for the benefit assessment of ciltacabtagene autoleucel to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 May 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 5 June 2023.

The oral hearing was held on 26 June 2023.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 21 July 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI

umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 25 July 2023, and the proposed resolution was approved.

At its session on 17 August 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 3 May 2023 | Information of the benefit assessment of the G-BA |
| Working group Section 35a | 20 June 2023 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal products | 26 June 2023 | Conduct of the oral hearing |
| Working group Section 35a | 5 July 2023<br>2 August 2023 | Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure |
| Subcommittee Medicinal products | 8 August 2023 | Concluding discussion of the draft resolution |
| Plenum | 17 August 2023 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 17 August 2023

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

Prof. Hecken