Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 17 August 2023, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Ciltacabtagene autoleucel as follows:

Ciltacabtagene autoleucel

Resolution of: 17 August 2023
Entry into force on: 17 August 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 25 May 2022):

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 17 August 2023):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Ciltacabtagene autoleucel 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. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

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.

Extent of the additional benefit and significance of the evidence of ciltacabtagene autoleucel:

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

Study results according to endpoints:[1]

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.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

CARTITUDE-1 study: open-label, single-arm phase Ib/II study (data cut-off: 11.01.2022)

CARTITUDE-4 study (presented additionally): randomised controlled trial (N = 516): Ciltacabtagene autoleucel vs pomalidomide, bortezomib and dexamethasone (PVd) or daratumumab, pomalidomide and dexamethasone (DPd); sub-population of patients with three prior therapies (N = 49); (data cut-off: 01.11.2022)

Mortality

CARTITUDE-1, ITT population		
Endpoint	N	*Patients with event n (%)*
Overall survival	124	39 (31.5)
Overall survival rate		*Kaplan-Meier estimator (%) [95% CI]*
At month 12	124	82.86 [74.69; 88.6]
At month 24	124	73.9 [64.83; 81.0]
		KM median (in months) [95% CI]
	124	n.r. [31.47; n.r.]

[1] Data from the dossier assessment of the G-BA (published on 15. Mai 2023), unless otherwise indicated.

CARTITUDE-4 (presented additionally)					
Endpoint	Ciltacabtagene autoleucel		Pomalidomide, bortezomib and dexamethasone (PVd) or daratumumab, pomalidomide and dexamethasone (DPd)		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value
Overall survival					
	20	n.r. [19.15; n.c.] 4 (20.0)	29	15.7 [14.85; n.c.] 11 (37.9)	0.42 [0.13; 1.32] 0.14

Morbidity

CARTITUDE-1 study, ITT population		
Progression-free survival (PFS)[a)]	**N**	
Patients with event n (%)	124	61 (49.2%)
Median [CI] (months)	124	27.43 [19.32; NA]
Overall response rate		*Patients with event n (%)*
Complete response (≥ CR)	124	83 (66.9)
Overall response rate (≥ PR)[b)]	124	103 (83.1)
CARTITUDE-1 study, PRO population[c)]		
Endpoint	**N**	*Mean value (SD)*
Change EQ-5D-VAS[d)]		
Screening Day 100 after infusion	90	69.65 (20.0) 73.02 (18.4)
Change in symptom scales of the EORTC QLQ-C30[e)]		
Fatigue Screening Day 100 after infusion	90	 38.29 (26.4) 35.10 (23.1)
Nausea and vomiting Screening Day 100 after infusion	90	 6.43 (11.6) 6.35 (13.2)
Pain Screening Day 100 after infusion	90	 35.34 (31.6) 24.87 (26.7)
Dyspnoea Screening	90	 17.67 (23.5)

Day 100 after infusion		15.59 (23.9)
Insomnia Screening *Day 100 after infusion*	90	 26.1 (28.5) 25.4 (28.5)
Loss of appetite Screening *Day 100 after infusion*	90	 16.87 (25.7) 19.04 (25.9)
Constipation Screening *Day 100 after infusion*	90	 13.24 (20.1) 6.30 (13.2)
Diarrhoea Screening *Day 100 after infusion*	90	 17.1 (24.87) 18.97 (28.2)

Health-related quality of life

CARTITUDE-1 study, PRO population[c)]		
Change in quality of life scales of the EORTC QLQ-C30[f)]		
General health status Screening Day 100 after infusion	90	 62.1 (21.9) 65.5 (20.5)
Physical functioning Screening Day 100 after infusion	90	 77.8 (22.84) 77.7 (21.09)
Role functioning Screening Day 100 after infusion	90	 72.9 (29.76) 72 (26.24)
Social functioning Screening Day 100 after infusion	90	 75.8 (27.5) 77.18 (25.44)
Cognitive functioning Screening Day 100 after infusion	90	 82.3 (19.55) 83.6 (19.8)
Emotional functioning Screening Day 100 after infusion	90	 81.1 (16.25) 88 (14.95)

Side effects

Endpoint	N	CARTITUDE-1, ITT population n (%)
Adverse events (AEs) in total	124	123 (99.2)
Serious adverse events (SAE)	124	78 (62.9)
Severe adverse events (CTCAE grade ≥ 3)	124	118 (95.2)
Severe AEs with incidence ≥ 5% at PT level		
MedDRA system organ class Preferred term		
Blood and lymphatic system disorders[g)]	**124**	**116 (93.5)**
Anaemia	124	87 (70.2)
Febrile neutropenia	124	18 (14.5)
Leukopenia	124	67 (54.0)
Lymphopenia	124	63 (50.8)
Neutropenia	124	108 (87.1)
Thrombocytopenia	124	74 (59.7)
Cardiac disorders	124	**8 (6.5)**
Gastrointestinal disorders	**124**	9 (7.3)
General disorders and administration site conditions	**124**	**11 (8.9)**
Fatigue	124	9 (7.3)
Infections and infestations[g)]	**124**	30 (24.2)
Pneumonia	**124**	12 (9.7)
Sepsis	124	9 (7.3)
Investigations	**124**	**22 (17.7)**
Aspartate aminotransferase increased	124	10 (8.1)
Gamma-glutamyltransferase increased	124	7 (5.6)
Metabolism and nutrition disorders	**124**	29 (23.4)
Hypophosphataemia	124	9 (7.3)
Hyponatremia	124	7 (5.6)
Musculoskeletal and connective tissue disorders	**124**	11 (8.9)
Nervous system disorders	**124**	12 (9.7)
Renal and urinary disorders	**124**	7 (5.6)
Acute kidney injury	124	7 (5.6)
Respiratory, thoracic and mediastinal disorders	**124**	11 (8.9)

Vascular disorders	**124**	**13 (10.5)**
Hypertension	124	9 (7.3)
Serious adverse events (SAEs) with incidence ≥ 5%		
Blood and lymphatic system disorders[g)]	**124**	**12 (9.7)**
Febrile neutropenia	124	7 (5.6)
Cardiac disorders	**124**	**8 (6.5)**
General disorders and administration site conditions	**124**	**11 (8,9)**
Immune system disorders	124	21 (16.9)
Cytokine release syndrome[g), h)]	124	21 (16.9)
Infections and infestations[g)]	**124**	**34 (27.4)**
Pneumonia	124	9 (7.3)
Sepsis	124	7 (5.6)
Nervous system disorders	**124**	**17 (13.7)**
Respiratory, thoracic and mediastinal disorders	124	**13 (10.5)**
AEs of special interest grade ≥ 3		
Cytokine release syndrome[h)]	124	5 (4.0)
Neurotoxicity[h)]	124	16 (12.9)
Cytopenia	124	116 (93.5)
Infections	124	30 (24.2)

CARTITUDE-4 (presented additionally)

Endpoint	Ciltacabtagene autoleucel		Pomalidomide, bortezomib and dexamethasone (PVd) or daratumumab, pomalidomide and dexamethasone (DPd)		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Hazard ratio [95% CI] p value
Adverse events (AEs) in total	20	20 (100)	27	27 (100)	-
Serious adverse events (SAEs)[i)]	20	11 (55.0)	27	9 (33.3)	1.87 [0.76; 4.56] 0.17
Severe adverse events (CTCAE grade ≥ 3)	20	20 (100)	27	25 (92.6)	1.45 [0.79; 2.69] 0.24
Therapy discontinuation due to AEs	20	n.d.	27	n.d.	n.d.

[a] Information from the dossier of the pharmaceutical company.
[b] Primary endpoint of the CARTITUDE-1 study.
[c] Subjects in the phase II part of the study for whom morbidity has been assessed by questionnaires.
[d] Values from 0 to 100; higher values correspond to better health status.
[e] Values from 0 to 100; higher values correspond to more severe disease symptomatology.
[f] Values from 0 to 100; higher values correspond to better functioning or health/ quality of life.
[g] AEs of special interest in the CARTITUDE-1 study.
[h] Classification according to Lee et al. 2019.
[i] In the ciltacabtagene autoleucel arm, SAEs were completely recorded throughout. In the DPd/ PVd arm, only SAEs considered related to the study medicine were recorded from 30 days after the end of treatment.

Indication of absolute difference (AD) only in case of statistically significant difference; own calculation

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-VAS = visual analogue scale of the European Quality of Life 5-Dimension; HR = hazard ratio; ITT = Intention-to-Treat; CI = confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PRO = Patient Reported Outcome; QLQ-C30 = Quality of Life Questionnaire - Core Questionnaire; AE(SI) = adverse event (of special interest); SD = standard deviation; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

approx. 1,210 - 1,310 patients

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: 28 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.

4. Treatment costs

Annual treatment costs:

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.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ciltacabtagene autoleucel[2,3,4]	€ 420,000
Additionally required SHI services	€ 763.07

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 August 2023)

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Prior chemotherapy for lymphocyte depletion					
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300

[2] Ciltacabtagene autoleucel is used once only
[3] It concerns only the cost of the medicinal product Carvykti
[4] Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 Medicinal Products Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed.

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**

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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.

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

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 17 August 2023.

1. The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.
2. The period of validity of the resolution is limited to 1 July 2026.

Berlin, 17 August 2023

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

Prof. Hecken