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
Idecabtagen vicleucel (multiple myeloma, at least 3 prior therapies)

of 16 June 2022

At its session on 16 June 2022, 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 Idecabtagen vicleucel as follows:

Idecabtagen vicleucel

Resolution of: 16 June 2022
Entry into force on: 16 June 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 18 August 2021):

Abecma 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 16 June 2022):

See therapeutic indication according to marketing authorisation.

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

Idecabtagen vicleucel 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 Idecabtagen vicleucel:

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.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

- KarMMa study: open-label, single-arm, multicentre, multinational phase II study; data cut-off from 21 December 2020
- CRB-401 study: open-label, two-part, single-arm, multicentre phase I study; data cut-off from 7 April 2020
- Sub-population of the KarMMa and CRB-401 studies compliant with marketing authorisation (adults who received a target dose of viable CAR+ T cells of 260 – 500 x 10^6 compliant with marketing authorisation)

[1] Data from the dossier assessment of the G-BA (published on 1. April 2022), unless otherwise indicated.

Mortality

Endpoint	Idecabtagen vicleucel (Ide-Cel)	
	N	Median survival time in months [95% CI] *Patients with event n (%)*
Overall survival (OS)		
CRB-401	42	n.a.[a] *12 (28.6)*
KarMMa	136	23.3 [20.2; 32.1][b] *69 (50.7)*

Morbidity

Endpoint	Idecabtagen vicleucel (Ide-Cel)	
	N	Median time in months [95% CI] *Patients with event n (%)*
Progression-free survival (PFS)[c]		
CRB-401	42	9.9 [7.3; 12.9] *34 (81.0)*
KarMMa	136	9.1 [6.7; 12.0] *111 (81.6)*
Endpoint	**Idecabtagen vicleucel (Ide-Cel)**	
	N[d]	Patients with event n (%)
KarMMa study: Health status (EQ-5D VAS) [e]		
No assessable data available.[f]		
KarMMa study: EORTC-QLQ-C30[g]		
No assessable data available.[f]		
KarMMa study: EORTC-QLQ-MY20[g]		
No assessable data available.[f]		

Health-related quality of life

Endpoint	Idecabtagen vicleucel (Ide-Cel)	
	N[d]	Patients with event n (%)
KarMMa study: EORTC-QLQ-C30[h]		
No assessable data available.[f]		
KarMMa study: EORTC-QLQ-MY20[h]		
No assessable data available.[f]		

Side effects

Endpoint	Idecabtagen vicleucel (Ide-Cel)					
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
	Leukapheresis to lymphodepleting chemotherapy (LDC)[i]		Lymphodepleting chemotherapy (LDC) to Ide-Cel infusion		Ide-Cel infusion until end of follow-up[j,k]	
Serious adverse events (SAE)						
KarMMa	136	30 (22.1)	124	8 (6.5)	124	86 (69.4)
CRB-401	42	7 (16.7)	38	1 (2.6)	38	29 (76.3)
Severe adverse events (CTCAE grade ≥ 3)						
KarMMa	136	48 (35.3)	124	67 (54.0)	124	123 (99.2)
CRB-401	42	13 (31.0)	38	25 (65.8)	38	37 (97.4)
Adverse events of special interest (AESI)						
Subjects with at least one AESI regardless of severity grade						
KarMMa	136	54 (39.7)	124	78 (62.9)	124	123 (99.2)
CRB-401	42	24 (57.1)	38	30 (78.9)	38	38 (100.0)
Subjects with ≥ 1 severe AESI ≥ grade 3						
KarMMa	136	39 (28.7)	124	69 (50.7)	124	122 (89.7)
CRB-401	42	11 (26.2)	38	24 (63.2)	38	36 (94.7)
Subjects with ≥ 1 serious AESI						
KarMMa	136	14 (10.3)	124	6 (4.4)	124	69 (50.7)
CRB-401	42	4 (9.5)	38	1 (2.6)	38	22 (57.9)

Endpoint	Idecabtagen vicleucel (Ide-Cel)					
	N	Patients with event n (%)				
	Leukapheresis to lymphodepleting chemotherapy (LDC)[i]		Lymphodepleting chemotherapy (LDC) to Ide-Cel infusion		Ide-Cel infusion until end of follow-up[j,k]	
Cytokine release syndrome						
KarMMa	136	0	124	0	124	105 (84.7)
CRB-401	42	0	38	0	38	35 (92.1)
Cytopenia – total						
KarMMa	136	41 (30.1)	124	71 (57.3)	124	120 (96.8)
CRB-401	42	18 (42.9)	38	27 (71.1)	38	35 (92.1)
Infections – total						
KarMMa	136	13 (9.6)	124	8 (6.5)	124	87 (70.2)
CRB-401	42	3 (7.1)	38	4 (10.5)	38	29 (76.3)
New malignancy						
KarMMa	136	0	124	0	124	9 (7.3)
CRB-401	42	0	38	0	38	5 (13.2)
Macrophage activation syndrome						
KarMMa	136	0	124	0	124	4 (3.2)
CRB-401	42	0	38	0	38	0
Neurological toxicity – broad[l]						
KarMMa	136	10 (7.4)	124	31 (25.0)	124	87 (70.2)
CRB-401	42	9 (21.4)	38	9 (23.7)	38	33 (86.8)
Neurological toxicity – focused[m]						
KarMMa	136	0	124	0	124	51 (41.1)
CRB-401	42	3 (7.1)	38	1 (2.6)	38	20 (52.6)

a Median survival is not considered valid and is not included due to multiple censoring and a very short median observation period of about 17 months compared to the magnitude of the overall survival estimator (35 months), and because there was no follow-up of overall survival beyond disease progression in about 23% of subjects in the CRB-401 study.
b Time from enrolment in the study or from leukapheresis to death or censoring. Subjects who were alive at the time of the data cut-off were censored at the time of the last contact. Subjects who were demonstrably alive or deceased after the data cut-off were an exception; this was censored at the time of the data cut-off.
c Information from the dossier of the pharmaceutical company.
d PRO analysis kit: Subjects in the Ide-Cel population with at least one PRO assessment at baseline and post-baseline.
e Values from 0 to 100; higher values correspond to better health status.

f An assessment of the return rates related to all subjects who received leukapheresis and are still alive is not possible. In addition, no evaluations are available for the relevant patient population that received leukapheresis. Thus, patients who experienced disease progression after leukapheresis and before Ide-Cel infusion or who discontinued the study before Ide-Cel infusion are not included in the evaluations presented. Therefore, the evaluations are not considered usable.

g Values from 0 to 100; higher values correspond to more severe disease symptomatology.

h Values from 0 to 100; higher values correspond to better functioning or health/ quality of life.

i In the KarMMa study, only intervention-related AEs and any SAEs were recorded before lymphodepleting chemotherapy (LDC). In the CRB-401 study, all AEs were fully recorded from leukapheresis until 24 months after infusion with Ide-Cel or until disease progression.

j In the KarMMa study, after receiving the 1st dose of LDC, adverse events (AEs) were only fully recorded up to and including month 6 after infusion with Ide-Cel. Subsequently, only AEs ≥ grade 3, serious adverse events (SAEs) and adverse events of special interest (AESI) were recorded until month 24 or the end of the study. In subjects without progression, all AEs ≥ grade 3, SAEs and AESI were recorded from month 24 onwards, each with reference to the study medication until the end of study participation or progression for up to 5 years. Data from the long-term follow-up GC-LTFU-001 study included (data cut-off from 21.12.2020). AEs that occurred during or after a repeat Ide-Cel infusion were not considered. Signs and symptoms of neurotoxicity identified by study personnel were coded as AEs and the evaluations integrated. Information from module 4 of the benefit dossier.

k For the CRB-401 study, according to Protocol Amendment 5.0, in the case of disease progression before month 6, all AEs were reported until month 6 after infusion with Ide-Cel. Up to month 24, all AEs were completely recorded. After month 24, coverage was restricted to AEs ≥ grade 3, SAEs and AESI. For subjects who crossed over to the long-term follow-up LTF-305 studies, AEs were collected analogous to the CRB-401 study, with "late" onset AEs and AESI to be additionally recorded annually from month 60 to year 15. In the CG-LTFU-001 study, all AEs with a possible relation to the study medication will be collected for up to 15 years.

l All AEs according to PT within the system organ classes "Nervous system disorders" and "Psychiatric disorders".

m Selected PT of neurotoxicological events determined by the pharmaceutical company considering the biological/pharmacological plausibility of a relationship between the medicinal product and event. Known neurotoxicities that are reported in association with this class of medicinal products and are consistent with published recommendations regarding CAR-T encephalopathy, and according to clinical assessment.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire - Core 30; EORTC QLQ-MY20 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire - Multiple Myeloma 20; EQ-5D-VAS = European Quality of Life Visual Analogue Scale - 5 Dimensions; HR = hazard ratio; Ide-Cel = idecabtagen vicleucel; CI = confidence interval; LDC = conditioning chemotherapy; PRO = patient-reported outcome; PT = preferred term; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; (S)AE = (serious) adverse event; AESI = adverse events of special interest; vs = versus

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

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.

approx. 1,200 – 1,300 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 Abecma (active ingredient: idecabtagen vicleucel) at the following publicly accessible link (last access: 2 May 2022):

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

This medicinal product was authorised 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.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient emergency card. Training material for all healthcare professionals who will prescribe, dispense, and administer idecabtagen vicleucel 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 idecabtagen vicleucel, and to carry the patient emergency card at all times.

Idecabtagen vicleucel must be used in a qualified treatment centre. For the infusion of idecabtagen vicleucel in multiple myeloma diagnosed with C90.00 and C90.01, the quality assurance measures for the use of CAR-T cells in B-cell neoplasms apply (ATMP Quality Assurance Guideline, Annex 1).

There is limited experience of re-treatment of patients with a second dose of Abecma. The response to re-treatment with Abecma was irregular and of shorter duration compared to the first treatment. In addition, fatal courses were observed in patients who were retreated.

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
Idecabtagen vicleucel[2]	€ 350,000
Additionally required SHI services:[3]	
Lymphocyte depleting chemotherapy	€ 726.51

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2022)

Other SHI services:

Designation of the therapy	Type of service	Unit cost	Number per cycle	Number per patient per year	Costs per patient per year
Lymphocyte depletion					
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	3	€ 243
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	3	€ 243

[2] It concerns only the cost of the medicinal product Abecma®.

[3] 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 June 2022.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 16 June 2022

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

Prof. Hecken