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
Brexucabtagen Autoleucel (new therapeutic indication: relapsed or refractory B-cell precursor acute lymphoblastic leukaemia, 26 years of age and above)

of 16 March 2023

At its session on 16 March 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. In Annex XII, the following information shall be added to the information on the restriction of the authority to supply care of Brexucabtagen Autoleucel according to the resolution of 21 July 2022 after the explanations on the restriction of the authority to supply care according to Section 35a, paragraph 3b, sentence 2 SGB V:

Brexucabtagen autoleucel

Resolution of: 16 March 2023
Entry into force on: 16 March 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 2 September 2022):

Tecartus is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

Therapeutic indication of the resolution (resolution of 16 March 2023):

See new therapeutic indication according to marketing authorisation.

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

Brexucabtagen 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).

<u>Adults 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)</u>

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

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

Study results according to endpoints:[1]

Adults 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)

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	∅	No data available.
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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

ZUMA-3: single-arm phase I/II study (data cut-off: 23.07.2021)

Mortality

Endpoint	ZUMA-3 (FAS)	
	N	*Patients with event n (%)*
Overall survival	81	41 (50.6)
Overall survival rate		*Kaplan-Meier estimator (%) [95% CI]* [a)]
at month 6	81	70.9 [59.2; 79.8]
at month 12	81	64.0 [52.0; 73.7]
at month 18	81	52.7 [40.7; 63.4]
at month 24	81	48.2 [36.3; 59.1]
		KM median (in months)[b)] *[95% CI]*
	81	23.1 [13.5; n.r.]

[1] Data from the dossier assessment of the G-BA (published on 2. January 2023), unless otherwise indicated.

Morbidity

Endpoint	ZUMA-3 (FAS)			
	N	*Patients with event n (%) [95% CI][c)]* Central assessment[d)]	**N**	*Patients with event n (%) [95% CI][c)]* Medical investigators
Overall complete remission				
Overall complete remission (OCR)	58	31 (53.4) [40; 67]	81	47 (58.0) [47; 69]
Complete remission (CR)	58	24 (41.4) [29; 55]	81	39 (48.1) [37; 60]
Complete remission with incomplete haematological recovery (CRi)	58	7 (12.1) [5; 23]	81	8 (9.9) [4; 19]
MRD negativity (presented additionally)				
Total MRD-negative rate	58	34 (59) [45; 71]	81	51 (63) [52; 73
	N	*Event-free time (in months) Median [95% CI] (min; max)*		
Duration of response				
	47	13.7 [9.4; n.r.] (0.03+; 24.08)		
EQ-5D-VAS				
There are no usable data.				

Health-related quality of life

Was not assessed in the ZUMA-3 study.

Side effects

Endpoint	ZUMA-3 FAS total[e)] *n (%)*		ZUMA-3 SAS[f)] *n (%)*		ZUMA-3 FAS without infusion[g)] *n (%)*	
	N	*Patients with at least one event n (%)*	N	*Patients with at least one event n (%)*	N	*Patients with at least one event n (%)*
Adverse events in total						
	81	78 (96)	63	63 (100)	18	15 (83)

Endpoint	ZUMA-3 FAS total[e)] *n (%)*		ZUMA-3 SAS[f)] *n (%)*		ZUMA-3 FAS without infusion[g)] *n (%)*	
	N	*Patients with at least one event n (%)*	N	*Patients with at least one event n (%)*	N	*Patients with at least one event n (%)*
Serious adverse events (SAEs)						
	81	64 (79)	63	49 (78)	18	12 (67)
Severe adverse events (CTCAE grade 3 or 4)						
	81	77 (95)	63	61 (97)	18	14 (78)
No treatment due to adverse events [h)]						
	81	-	63	-	18	9 (50)

MedDRA system organ class Preferred term	**N**	**ZUMA-3** ***n (%)***
AE ≥ grade 3 with incidence ≥ 5% at PT level		
Blood and lymphatic system disorders	**63**	**45 (71)**
Anaemia[i)]	63	32 (51)
Neutropenia[i)]	63	11 (17)
Thrombocytopenia[i)]	63	7 (11)
Cardiac disorders	63	**4 (6)**
Gastrointestinal disorders	**63**	**7 (11)**
General disorders and administration site conditions	**63**	**26 (41)**
Pyrexia	63	24 (38)
Infections and infestations[i)]	**63**	**17 (27)**
Investigations	**63**	**36 (57)**
Thrombocytopenia	63	20 (32)
Neutropenia	63	19 (30)
Alanine aminotransferase increased	63	7 (11)
Aspartate aminotransferase increased	63	7 (11)
Leukopenia	63	12 (19)
Metabolism and nutrition disorders	**63**	**26 (41)**
Hypophosphataemia	63	18 (29)
Hypokalaemia	63	5 (8)

MedDRA system organ class Preferred term	**N**	**ZUMA-3** ***n (%)***
Hyperglycaemia	63	5 (8)
Hypocalcaemia	63	4 (6)
Musculoskeletal and connective tissue disorders	**63**	**4 (6)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**63**	**5 (8)**
Nervous system disorders [i)]	**63**	**18 (29)**
Encephalopathy	63	8 (13)
Aphasia	63	8 (13)
Psychiatric disorders	**63**	**5 (8)**
Respiratory, thoracic and mediastinal disorders	**63**	**19 (30)**
Hypoxia	63	15 (24)
Vascular disorders	**63**	**25 (40)**
Hypotension	63	22 (35)
Hypertension	63	4 (6)
SAE (grade 3 or higher) with incidence ≥ 5% at PT level		
Blood and lymphatic system disorders	**63**	**5 (8)**
Cardiac disorders	63	7 (11)
Tachycardia	63	4 (6)
Gastrointestinal disorders	**63**	**5 (8)**
General disorders and administration site conditions	**63**	**16 (25)**
Pyrexia	63	16 (26)
Infections and infestations[i)]	**63**	**17 (27)**
Blood poisoning	63	6 (10)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	63	**6 (10)**
Acute lymphatic leukaemia	63	5 (8)
Nervous system disorders [i)]	**63**	**20 (32)**
Encephalopathy	63	9 (14)
Aphasia	63	5 (8)
Psychiatric disorders	**63**	**5 (8)**
Confused state	63	4 (6)

MedDRA system organ class Preferred term	**N**	**ZUMA-3** ***n (%)***
Respiratory, thoracic and mediastinal disorders	**63**	**11 (17)**
Hypoxia	63	8 (13)
Vascular disorders	63	**23 (37)**
Hypotension	63	23 (37)
Adverse events of special interest (AESI)		
Important identified risks		
Cytokine release syndrome[j)]	63	16 (25)
Neurologic events[k)]	63	18 (29)
Cytopenia	63	26 (41)
Infections	63	17 (27)
Potential risks		
Graft-versus-host disease	63	1 (2)
Cytopenias		
Thrombocytopenia	63	26 (41)
Neutropenia	63	35 (56)
Anaemia	63	32 (51)
Other AEs of special interest		
Arrhythmia	63	4 (6)
Heart failure	63	2 (3)

a) The probability of a subject surviving until the specified time was determined using Kaplan-Meier methodology (Kaplan-Meier estimator). It is unclear which formula has been used for the calculation.
b) Median duration of overall survival. For subjects who have survived the relevant data cut-off, the survival time at the last known point of survival time is censored.
c) Calculated according to Clopper Pearson (data from the dossier of the pharmaceutical company).
d) The phase II cohort is presented due to differences in the survey between phase I and phase II and unclear effects of missing study subjects from the phase I cohort who did not undergo a central assessment.
e) All subjects enrolled in the study, regardless of the respective study phase.
f) All subjects enrolled in the study who received an infusion, regardless of the respective study phase.
g) All subjects who were enrolled in the study but did not receive an infusion.
h) Study subjects received bridge therapy and lymphocyte depletion chemotherapy between enrolment in the study and infusion.

i) These AEs are AESI.
j) Incidence and grading of severity using CRS Grading Scale according to Lee et al (2014).
k) Classification using modified criteria according to Topp (2015).

Abbreviations used:
AD = absolute difference; alloSCT = allogeneic stem cell transplantation; CR = complete remission; CRi = complete remission with incomplete haematological recovery; CTCAE = Common Terminology Criteria for Adverse Events; FAS = Full Analysis Set; HR = hazard ratio; KM = Kaplan-Meier; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; SAS = Safety Analysis Set; (S)AE = (serious) adverse events; AESI = adverse event of special interest; vs = versus
'+' marks censoring

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

approx. 81 – 200 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 Tecartus (active ingredient: brexucabtagen autoleucel) at the following publicly accessible link (last access: 8 February 2023):

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

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.
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 brexucabtagen 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 brexucabtagen autoleucel, and to carry the patient emergency card at all times.

Brexucabtagen 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

brexucabtagen-autoleucel in the therapeutic indication B-cell precursor ALL. Annex I CAR-T cells in B-cell neoplasms of the ATMP Quality Assurance Guideline provides further details.

4. Treatment costs

Annual treatment costs:

Adults 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Brexucabtagen autoleucel	€ 282,000.00
Additionally required SHI services	€ 405.35

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

Other SHI services:

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

5. 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 Brexucabtagen Autoleucel

Medicinal products with the following new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients, which, on the basis of the marketing authorisation granted under Medicinal Products Act, can be used in a combination therapy with brexucabtagen autoleucel for the treatment of B-cell precursor ALL:

- No active ingredient 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 16 March 2023.

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

Berlin, 16 March 2023

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

Prof. Hecken