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: Blinatumomab (new therapeutic indication: acute lymphoblastic B-cell leukaemia, high-risk first relapse, Ph-, CD19+, ≥1 and <18 years)

of 20 January 2022

At its session on 20 January 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. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Blinatumomab in accordance with the resolution of 15 July 2021:

Blinatumomab

Resolution of: 20 January 2022
Entry into force on: 20 January 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 24 June 2021):

Blincyto is indicated as monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy.

Therapeutic indication of the resolution (resolution of 20 January 2022):

See new therapeutic indication according to marketing authorisation.

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

Blinatumomab is approved as a medicinal product for the treatment of rare diseases in accordance with 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 German Social Code, Book Five (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>Paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy</u>

Extent of the additional benefit and significance of the evidence of Blinatumomab:

Indication of a considerable additional benefit

Study results according to endpoints:[1]

Paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantage in event-free survival
Health-related quality of life	∅	No data available.
Side effects	↑	Advantages in the endpoints of severe and serious AE

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

[1] Data from the dossier assessment of the G-BA (published on the 1. November 2021), unless otherwise indicated.

20120215 study: blinatumomab **vs** HC (high-risk consolidation chemotherapy)

- ongoing, multicentre, randomised, controlled, open-label, phase III study
- Data cut-offs used:

  Data cut-off for the interim study report: 17.07.2019[2]

  Data cut-off for overall survival: 14.09.2020[3]

Mortality

Endpoint	**Blinatumomab**		**HC3**		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 Absolute difference (AD)[a]
Overall survival					
Data cut-off of 17 July 2019	54	n.c. [n.c.; n.c.] 8 (14.8)	54	n.c. [15.7; n.c.] 16 (29.6)	0.43 [0.18; 1.01] 0.047
Data cut-off of 14 September 2020	54	n.c. [n.c.; n.c.] 9 (16.7)	57[b]	n.c. [17.5; n.c.] 23 (40.4)	0.33 [0.15; 0.72] 0.003

[2] A priori, two interim analyses were planned for the study. The first interim analysis was conducted at the time of approximately 50% and the second at the time of approximately 75% of the occurred events in the assessment of the primary endpoint of EFS. The second interim analysis was not conducted as the endpoint was reached after the first interim analysis.

[3] In addition to the predefined analyses, an additional data cut-off was made in consultation with the EMA to assess the secondary endpoint of overall survival. This took place on 14.09.2020 and is presented in addition to the data from the primary analysis on 17.07.2019.

Morbidity

Endpoint	**Blinatumomab**		**HC3**		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 Absolute difference (AD)[a]
Event-free survival (EFS)					
Data cut-off of 17 July 2019	54	n.a. [24.4; n.a.] 17 (31.5)	54	7.6 [4.5; 12.7] 31 (57.4)	0.33 [0.18; 0.61] < 0.001
	N	n (%)	N	n (%)	
EFS events	54	17 (31.5)	54	31 (57.4)	
Isolated bone marrow relapse	54	6 (11.1)	54	12 (22.2)	
Death from any cause	54	4 (7.4)	54	2 (3.7)	
M2 bone marrow after CR	54	4 (7.4)	54	12 (22.2)	
Combined bone marrow relapse	54	2 (3.7)	54	0	
CNS extra-medullary relapse	54	1 (1.9)	54	2 (3.7)	
Extra-medullary relapse elsewhere	54	0	54	3 (5.6)	
No CR after treatment with test substance	54	0	54	0	
Secondary malignancy	54	0	54	0	
	N	n (%)	N	n (%)	
Testicular extra-	54	0	54	0	

medullary relapse					
Endpoint	**Blinatumomab**		**HC3**		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 (%)*	Relative risk [95% CI] p value Absolute difference (AD)[a]
MRD remission (presented additionally)					
Data cut-off from 17 July 2019; MRD remission according to PCR	49[c]	44 (89.8)	48[c]	26 (54.2)	1.4 [1.1; 1.8] 0.017
Data cut-off from 17 July 2019; MRD remission according to flow cytometry	53[c]	48 (90.6)	53[c]	32 (60.4)	1.5 [1.1; 1.9] 0.003

Health-related quality of life

No data available.

Side effects

Endpoint	Blinatumomab		HC3		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
Data cut-off from 17 July 2019	54	- 54 (100)	51[d]	- 49 (96.1)	-
Serious adverse events (SAE)					
Data cut-off from 17 July 2019	54	n.c. [n.c.; n.c.] 13 (24.1)	51[d]	n.c. [0.49; n.c.] 22 (43.1)	0.49 [0.24; 0.98] 0.035
Severe adverse events (CTCAE grade ≥ 3)					
Data cut-off of 17 July 2019	54	1.70 [1.31; n.c.] 31 (57.4)	51[d]	0.26 [0.16; 0.33] 42 (82.4)	0.41 [0.25; 0.67] < 0.001 AD: + 1.44 months
Therapy discontinuation due to adverse events					
Data cut-off of 17 July 2019	54	n.c. [n.c.; n.c.] 2 (3.7)	51[d]	n.c. [n.c.; n.c.] 0 (0)	n.c. [n.c.; n.c.] 0.17
Severe AE of CTCAE grade ≥ 3 with an incidence ≥ 5% SOC					
Blood and lymphatic system disorders	54	n.c. [n.c.; n.c.] 15 (27.8)	51[d]	0.33 [0.26; 0.39] 37 (72.5)	0.24 [0.13; 0.45] < 0.001
Investigations	54	n.c. [n.c.; n.c.] 12 (22.2)	51[d]	n.c. [n.c.; n.c.] 15 (29.4)	0.69 [0.32; 1.48] 0.33
General disorders and administration site conditions	54	n.c. [n.c.; n.c.] 10 (18.5)	51[d]	n.c. [n.c.; n.c.] 1 (2.0)	8.06 [1.03; 63.08] 0.018

Endpoint	Blinatumomab		HC3		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Infections and infestations	54	n.c. [2.00; n.c.] 10 (18.5)	51d	n.c. [n.c.; n.c.] 5 (9.8)	1.56 [0.53; 4.61] 0.42
Gastrointestinal disorders	54	n.c. [n.c.; n.c.] 6 (11.1)	51[d]	n.c. [n.c.; n.c.] 17 (33.3)	0.24 [0.09; 0.62] 0.002
Vascular diseases	54	n.c. [n.c.; n.c.] 4 (7.4)	51[d]	n.c. [n.c.; n.c.] 2 (3.9)	1.92 [0.34; 10.86] 0.45
Nervous system disorders	54	n.c. [n.c.; n.c.] 3 (5.6)	51[d]	n.c. [n.c.; n.c.] 0 (0)	n.c. [n.c.; n.c.] 0.12
Congenital, familial and genetic disorders	54	n.c. [n.c.; n.c.] 2 (3.7)	51[d]	n.c. [n.c.; n.c.] 4 (7.8)	0.37 [0.07; 2.06] 0.24
Hepatobiliary disorders	54	n.c. [n.c.; n.c.] 2 (3.7)	51[d]	n.c. [n.c.; n.c.] 6 (11.8)	0.31 [0.06; 1.56] 0.14
Respiratory, thoracic and mediastinal disorders	54	n.c. [n.c.; n.c.] 1 (1.9)	51[d]	n.c. [n.c.; n.c.] 3 (5.9)	0.33 [0.03; 3.17] 0.31
Serious AE (SAE) (incidence ≥ 5%) **SOC** PT					
Nervous system disorders	54	n.c. [n.c.; n.c.] 5 (9.3)	51[d]	n.c. [n.c.; n.c.] 1 (2.0)	4.82 [0.56; 41.74] 0.12
Infections and infestations	54	n.c. [n.c.; n.c.] 3 (5.6)	51[d]	n.c. [n.c.; n.c.] 4 (7.8)	0.61 [0.13; 2.75] 0.51

Endpoint	Blinatumomab		HC3		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Gastrointestinal disorders	54	n.c. [n.c.; n.c.] 1 (1.9)	51[d]	n.c. [n.c.; n.c.] 3 (5.9)	0.30 [0.03; 2.87] 0.27
Blood and lymphatic system disorders	54	n.c. [n.c.; n.c.] 0 (0)	51d	n.c. [n.c.; n.c.] 13 (25.5)	n.c. [n.c.; n.c.] < 0.001
Febrile neutropenia	54	n.c. [n.c.; n.c.] 0 (0)	51[d]	n.c. [n.c.; n.c.] 9 (17.6)	n.c. [n.c.; n.c.] 0.002
Neutropenia	54	n.c. [n.c.; n.c.] 0 (0)	51[d]	n.c. [n.c.; n.c.] 3 (5.9)	n.c. [n.c.; n.c.] 0.077
Adverse events of special interest PT					
Capillary leak syndrome	54	n.c. [n.c.; n.c.] 0 (0)	51[d]	n.c. [n.c.; n.c.] 1 (2.0)	n.c. [n.c.; n.c.] 0.32
Cytokine release syndrome	54	n.c. [n.c.; n.c.] 2 (3.7)	51[d]	n.c. [n.c.; n.c.] 1 (2.0)	2.27 [0.21; 25.15] 0.49
Decreased immunoglobulin levels	54	n.c. [n.c.; n.c.] 9 (16.7)	51[d]	n.c. [n.c.; n.c.] 6 (11.8)	1.37 [0.49; 3.86] 0.55
Elevated liver levels	54	n.c. [n.c.; n.c.] 7 (13.0)	51[d]	n.c. [n.c.; n.c.] 15 (29.4)	0.39 [0.16; 0.96] 0.033
Embolic and thrombotic events	54	n.c. [n.c.; n.c.] 4 (7.4)	51[d]	n.c. [n.c.; n.c.] 0 (0)	n.c. [n.c.; n.c.] 0.037
Infections	54	n.c. [1.77; n.c.] 23 (42.6)	51[d]	n.c. [n.c.; n.c.] 16 (31.4)	1.02 [0.54; 1.94] 0.95

Endpoint	**Blinatumomab**		**HC3**		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Infusion reactions without consideration of the infusion duration	54	0.07 [0.03; 0.07] 37 (68.5)	51[d]	n.c. [n.c.; n.c.] 4 (7.8)	18.37 [5.62; 60.00] < 0.001
Medication errors	54	n.c. [n.c.; n.c.] 1 (1.9)	51[d]	n.c. [n.c.; n.c.] 0 (0)	n.c. [n.c.; n.c.] 0.34
Neurologic events	54	n.c. [0.20; n.c.] 26 (48.1)	51d	n.c. [n.c.; n.c.] 15 (29.4)	1.98 [1.04; 3.78] 0.037
Neutropenia and febrile neutropenia	54	n.c. [n.c.; n.c.] 12 (22.2)	51[d]	0.49 [0.36; n.c.] 28 (54.9)	0.36 [0.18; 0.71] 0.002
Pancreatitis	54	n.c. [n.c.; n.c.] 0 (0)	51[d]	n.c. [n.c.; n.c.] 1 (2.0)	n.c. [n.c.; n.c.] 0.31

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] In the HC3 arm, there are three more subjects in the study arm at the time of the second data cut-off than at the first DCO. It is assumed that three more subjects were enrolled in the HC3 arm between the first data cut-off on 17 July 2019 and the early enrolment stop following the DMC's recommendation in August 2019. Assuming that the three additional subjects in the HC3 arm were enrolled at the second data cut-off under the same study conditions (including stratified randomisation) and underwent the same study procedures as the previously enrolled patients, no hint for any risk of bias is seen
[c] Percentage of subjects with available MRD marker at baseline, N
[d] The safety analysis set (SAS) included all randomised patients who had received protocol-specified therapy and were analysed according to their treatment received (blinatumomab: n = 54; HC3: n = 51; in the HC3 group, 3 patients did not receive their assigned treatment)

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with event; n.c. = not calculable; n.a. = not achieved; SAE = serious adverse events; vs = versus

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

Paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy

approx. 7 to 30 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 Blincyto (active ingredient: blinatumomab) at the following publicly accessible link (last access: 29 November 2021):

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

Treatment with blinatumomab should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with acute lymphoblastic leukaemia, or specialists in paediatrics and adolescent medicine specialising in paediatric haematology and oncology.

In accordance with the requirements of the EMA regarding additional risk minimisation measures, the pharmaceutical company must provide training material for physicians, pharmacists, healthcare professionals and patients/ healthcare professionals, as well as a patient card.

In particular, the training material contains instructions on the administration of BLINCYTO and on neurological events.

4. Treatment costs

Annual treatment costs:

Paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Blinatumomab	€ 24,883.70 - € 69,674.36

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

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Blinatumomab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	10 - 28	10 - 28	€ 710 - € 1,988

I. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 January 2022.

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

Berlin, 20 January 2022

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

Prof. Hecken