Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Blinatumomab (new therapeutic indication: acute lymphatic leukaemia, MRD-positive patients)

of 15 August 2019

At its session on 15 August 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD 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 August 2019:

Blinatumomab

Resolution of: 15 August 2019
Entry into force on: 15 August 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 18 January 2019):

BLINCYTO is indicated as monotherapy for the treatment of adults with Philadelphia chromosome-negative, CD19-positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.

1. Extent of the additional benefit of the medicinal product

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. According to 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). 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).

Adult patients with Philadelphia chromosome-negative, CD19-positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.

Extent of the additional benefit:

Non-quantifiable

Study results according to endpoints:[1]

Adult patients with Philadelphia chromosome-negative, CD19-positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.

[1] Data from the dossier evaluation by the G-BA (published on 15 May 2019) unless indicated otherwise.

MT103-203 (BLAST) study

Mortality

Overall survival[b]	**N = 110[a]**
Deaths, n (%)	62 (56.4)
Survival time (months) Median [95% CI]	36.5 [22.0; n.a.]
Kaplan-Meier estimator	
after 60 months [95% CI]	0.43 [0.34; 0.52]

Morbidity

MRD remission	**N = 113[c]**
Complete MRD remission, n (%) [95% CI]	88 (77.9) [69.1; 85.1])
EQ-5D VAS[b, d]	**N = 103**
Absolute change □ *Treatment cycle 1 from baseline[e]*	
Mean (SD)	4.33 (21.17)
Median (min; max)	2.00 (−72.00; 90.80)
EORTC QLQ-C30[b, f]	**N = 102**
Absolute change □ *Treatment cycle 1 from baseline*	Mean (SD) Median (min; max)
Fatigue[g]	
	−0.50 (23.33) 0.00 (−66.67; 66.67)
Nausea and vomiting[g]	
	−0.56 (12.92) 0.00 (−66.67; 33.33)
Pain[g]	
	−2.25 (23.19) 0.00 (−83.33; 50.00)
Shortness of breath[h]	
	−2.65 (26.37) 0.00 (−100.00; 66.67)
Insomnia[g]	
	−0.75 (28.86) 0.00 (−66.67; 100.0)
Loss of appetite[g]	
	−1.87 (28.14) 0.00 (−66.67; 100.0)
Constipation[h]	
	0.38 (11.85)

	0.00 (−66.67; 33.33)
Diarrhoea[h]	
	1.52 (25.73) 0.00 (−100.0; 100.0)

Health-related quality of life

EORTC QLQ-C30[i]	**N = 102**
Absolute change □ *Treatment cycle 1 from baseline*	Mean (SD) Median (min; max)
General health status[h]	
	2.46 (18.49) 0.00 (−50.00; 58.33)
Bodily function[g]	
	0.30 (12.49) 0.00 (−33.33; 46.67)
Cognitive function[h]	
	−1.70 (16.19) 0.00 (−50.00; 50.00)
Emotional function[h]	
	4.20 (20.45) 0.00 (−66.67; 83.33)
Social function[h]	
	10.42 (31.80) 0.00 (−100.0; 100.0)
Role function[h]	
	−3.98 (30.01) 0.00 (−83.33; 100.0)

Side effects

Certainty[j]	**N = 116**
Total rates	
AE, n (%)	116 (100)
AE CTCAE grade ≥ 3, n (%)	71 (61.2)
SAE, n (%)	73 (62.9)
AE that led to discontinuation of the trial drug, n (%)	20 (17.2)
Specific AE (SOC, PT)	
AE with CTCAE grade ≥ 3 and incidence ≥ 5%, n (%)	
Blood and lymphatic system disorders	28 (24.1)
Leukopenia	7 (6.0)
Neutropoenia	18 (15.5)
General disorders and administration site conditions	15 (12.9)
Fever	9 (7.8)
Infections and infestations	12 (10.3)
Injury, poisoning and procedural complications	6 (5.2)
Investigations	21 (18.1)
Alanine aminotransferase increased	6 (5.2)
Nervous system disorders	16 (13.8)
Tremor	6 (5.2)
SAE with incidence ≥ 5%, n (%)	
Blood and lymphatic system disorders	8 (6.9)
General disorders and administration site conditions	25 (21.6)
Fever	17 (14.7)
Infections and infestations	15 (12.9)
Injury, poisoning and procedural complications	11 (9.5)
Investigations	9 (7.8)
Nervous system disorders	26 (22.4)
Encephalopathy	6 (5.2)
Tremor	8 (6.9)
Aphasia	6 (5.2)

Certainty[j]	N = 116

[a] This corresponds to the Population Key Sec EP FAS. This includes all patients of the FAS who were in haematological remission at the start of treatment with the exception of Ph-positive individuals
[b] Data cut-off: 7 January 2019; EQ-5D FAS or QLQ-C30 FAS
[c] Population of the Prim EP FAS includes all patients with an immunoglobulin TCR PCR MRD assay with a minimum sensitivity of 10^{-4} by a central laboratory at baseline
[d] Scale: 0–100; higher values mean a better health status
[e] n = 87
[f] Scales: 0–100; for the scales "fatigue", "nausea and vomiting", "pain", "shortness of breath", "insomnia", "loss of appetite", "constipation", and "diarrhoea", higher values correspond to more severe symptomatology.
[g] n = 89
[h] n = 88
[i] Scales: 0–100; for the scales "general condition/quality of life", "physical function", "cognitive function", "emotional function", "social function", and "role function", higher values correspond to a better condition or function. For the "financial difficulties" scale, higher values correspond to greater difficulties.
[j] Data cut-off: 5 August 2015

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D = EuroQol 5-dimensions questionnaire; FAS = full analysis set; CI = confidence interval; MRD = minimum residual disease; N = number of patients evaluated; n = number of patients with (at least one) event; n.a. = not achieved; PCR = polymerase chain reaction; PT = preferred term; AE = adverse events; SD = standard deviation; SOC = system organ class; SAE = serious AE; VAS = visual analogue scale

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

Adult patients with Philadelphia chromosome-negative, CD19-positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.

approx. 40 to 110 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: 10 May 2019):

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

Only specialists in internal medicine, haematology, and oncology experienced in the treatment of patients with acute lymphatic leukaemia may initiate and monitor treatment with blinatumomab.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material for doctors, pharmacists, medical specialists, and patients/nurses as well as a patient reminder card.

The training material contains, in particular, information on the administration of BLINCYTO® and on neurological events.

4. Treatment costs

Annual treatment costs:

Adult patients with Philadelphia chromosome-negative, CD19-positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.

Designation of the therapy	Annual treatment costs/patient
Blinatumomab	€ 73,260.60 – € 293,042.40

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2019)

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	a	€ 71	7	Induction 7 Consolidation 0–21	€ 497 – € 1,988
a: Supplement for the preparation of a parenteral solution containing monoclonal antibodies					

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 15 August 2019.

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

Berlin, 15 August 2019

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

Prof Hecken