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, paediatric patients aged 1 year or older)

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 7 December 2017:

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 23 August 2018):

BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome-negative, CD19-positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

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).

Paediatric patients aged 1 year or older with Philadelphia chromosome-negative, CD19-positive B-precursor ALL that is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

Extent of the additional benefit:

Non-quantifiable

Study results according to endpoints:[1]

Paediatric patients aged 1 year or older with Philadelphia chromosome-negative, CD19-positive B-precursor ALL that is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

Study MT103-205

Mortality

Overall survival	**FAS[a] N = 70**
Deaths, n (%)	48 (68.6)
Survival time (months) Median [95% CI]	7.5 [4.0; 11.8]

Morbidity

Complete remission	**FAS[a] N = 70**
Complete remission[b] within the first two cycles, n ((%) [95% CI]) CR CRh Complete remission without complete or partial recovery of the peripheral blood count	27 ((38.6) [27.2; 51.0]) 12 (17.1) 11 (15.7) 4 (5.7)
MRD remission	**FAS[a] N = 70**
Patients without MRD measurement, n (%)	8 (11.4)
Patients with MRD remission[d] within the first two cycles, n (%) [95% CI]	15 (21.4) [12.5; 32.9]
Patients with complete MRD remission[e] within the first two cycles, n (%) [95% CI]	15 (21.4) [12.5; 32.9]

Health-related quality of life

Not collected.

Side effects

Certainty[f]	**FAS[a] N = 70**
AE, n (%)	70 (100)
AE CTCAE grade ≥ 3, n (%)	61 (87.1)
SAE, n (%)	39 (55.7)

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

Certainty[f]	**FAS**[a] **N = 70**
AE that led to discontinuation of the trial drug, n (%)	4 (5.7)
Specific AE (SOC, PT)	
AE with CTCAE grade ≥ 3 and incidence ≥ 5%, n (%)	
Infections and infestations	18 (25.7)
Blood and lymphatic system disorders	38 (54.3)
Anaemia	25 (35.7)
Thrombocytopoenia	15 (21.4)
Febrile neutropenia	12 (17.1)
Neutropoenia	12 (17.1)
Leukopenia	7 (10.0)
Immune system disorders	6 (8.6)
Cytokine release syndrome	4 (5.7)
Metabolism and nutrition disorders	15 (21.4)
Hypokalemia	12 (17.1)
Nervous system disorders	6 (8.6)
Vascular disorders	4 (5.7)
Hypertension	4 (5.7)
Respiratory, thoracic, and mediastinal disorders	9 (12.9)
Gastrointestinal disorders	6 (8.6)
Musculoskeletal and connective tissue disorders	4 (5.7)
General disorders and administration site conditions	13 (18.6)
Pyrexia	10 (14.3)
Investigations	24 (34.3)
Alanine aminotransferase increased	11 (15.7)
Neutrophil number reduced	9 (12.9)
Aspartate aminotransferase increased	8 (11.4)
Thrombocyte number reduced	10 (14.3)
Leukocyte number reduced	7 (10.0)
SAE with incidence ≥ 5%, n (%)	
Infections and infestations	15 (21.4)
Blood and lymphatic system disorders	8 (11.4)
Febrile neutropenia	8 (11.4)
Immune system disorders	5 (7.1)
Cytokine release syndrome	4 (5.7)
Nervous system disorders	6 (8.6)

Certainty[f]	FAS[a] N = 70
Respiratory, thoracic, and mediastinal disorders	6 (8.6)
Gastrointestinal disorders	4 (5.7)
General disorders and administration site conditions	12 (17.1)
Pyrexia	8 (11.4)
Injury, poisoning and procedural complications	5 (7.1)

[a] Pooled FAS population from Phase I (n = 26) and II (n = 44)
[b] The endpoint complete remission contains the following three definitions: CR, Crh, and complete remission without complete or partial recovery of the peripheral blood count
[c] Two-sided exact 95% confidence interval
[d] Defined as MRD remission rate below 10^{-4} within two treatment cycles measured by PCR or flow cytometry.
[e] Defined as MRD remission rate below detection limit within two treatment cycles measured by PCR or flow cytometry.
[f] AE occurred between the start of therapy with blinatumomab until 30 days after completion of last infusion during the core study or AE occurred between the start of re-therapy with blinatumomab and 30 days after completion of last infusion during re-therapy

Abbreviations used:
CR = Complete remission with complete recovery of the peripheral blood count; CRh = Complete remission with partial recovery of the peripheral blood count; CTCAE = Common Terminology Criteria for Adverse Events; FAS = full analysis set; CI = confidence interval; MRD = minimal residual disease; N = number of patients evaluated; n = number of patients with (at least one) event; PCR = polymerase chain reaction; PT = preferred term; AE = adverse events; SOC = system organ class; SAE = serious AE

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

Paediatric patients aged 1 year or older with Philadelphia chromosome-negative, CD19-positive B-precursor ALL that is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

approx. 30 to 80 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 or specialists in paediatrics and adolescent medicine with a focus on haematology and oncology 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:

Paediatric patients aged 1 year or older with Philadelphia chromosome-negative, CD19-positive B-precursor ALL that is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

Designation of the therapy	Annual treatment costs/patient
Induction therapy	€ 49,712.55–136,055.40[2]
Consolidation therapy	€ 0–219,781.80[3]
Total	€ 49,712.55 – € 355,837.20

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	One-year-old child Cycle 1: 9 Cycle 2–5: 10 each 17-year-old: Cycle 1: 9 Cycle 2–5: 7 each	One-year-old child Induction 19 Consolidation 0–30 17-year-old adolescent Induction 16 Consolidation 0–21	One-year-old child € 1,349 – € 4,189 17-year-old adolescent € 1,136 – € 2,627

[2] Range taking into account the cost of two cycles of induction therapy for a one-year-old and a 17-year-old child.
[3] Range taking into account the cost of zero cycles of consolidation therapy and three cycles of consolidation therapy in a 17-year-old child.

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