Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Belimumab (New Therapeutic Indication: Systemic Lupus Erythematosus, ≥ 5 Years)

of 14 May 2020

At its session on 14 May 2020, 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 belimumab in accordance with the resolution of 2 August 2012 (Federal Gazette, BAnz AT 19 September 2012 B3):

Belimumab

Resolution of: 14 May 2020
Entry into force on: 14 May 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 21 October 2019):

Benlysta is indicated as add-on therapy in patients 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy (see section 5.1).

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Children and adolescents from 5 to 17 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy

Appropriate comparator therapy:

A patient-individual therapy, taking into account the respective organ attack, the previous therapy, and the disease activity and selecting amongst the following therapies:

- Hydroxychloroquine, chloroquine
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Glucocorticoids
- Azathioprine

Extent and probability of the additional benefit of belimumab as adjunctive therapy compared with a patient-individual therapy:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

Children and adolescents from 5 to 17 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy

[1] Data from the dossier assessment of the IQWiG (A19-97) and the addendum (A19-94) unless otherwise indicated.

PLUTO study: double-blind RCT; belimumab + patient-individual therapy **vs** placebo + patient-individual therapy; relevant sub-population: ITT-ZVT-2

PLUTO study Endpoint category Endpoint	Belimumab + concomitant medication		Placebo + concomitant medication		Belimumab + concomitant medication vs placebo + concomitant medication
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Mortality					
Overall mortality	21	0 (0.0)	14	0 (0.0)	not calculable
Morbidity and health-related quality of life					
No usable data					

PLUTO study Endpoint category Endpoint	Belimumab + concomitant medication		Placebo + concomitant medication		Belimumab + concomitant medication vs placebo + concomitant medication
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI]; p value
Morbidity					
SFI, severe flares (presented additionally)					
SFI, severe flares	21	n.a. 2 (9.5)	14	n.a. 6 (42.9)	0.16 [0.03; 0.81] 0.027
SFI, severe flares, sensitivity analysis 1[a]	21	1 (4.8)[b]	14	3 (21.4)[b]	RR: 0.22 [0.03; 1.93] [b] p = 0.155[d]
SFI, severe flares, sensitivity analysis 2[c]	21	0 (0)[b]	14	2 (14.3)[b]	RR: 0.14 [0.01; 2.65] [b] p = 0.091[b]

PLUTO study Endpoint category Endpoint	Belimumab + concomitant medication		Placebo + concomitant medication		Belimumab + concomitant medication vs placebo + concomitant medication
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value

Side effects[d]					
AEs (additionally shown)	21	14 (66.7)	14	12 (85.7)	–
SAEs	21	1 (4.8)	14	6 (42.9)	0.11 [0.01; 0.83] 0.007
Discontinuation because of AEs	21	0 (0.0)	14	1 (7.1)	not calculated
Infections and infestations (AEs, SOC)	21	8 (38.1)	14	12 (85.7)	0.50 [0.29; 0.86] 0.006

a: Sensitivity analysis without consideration of patients in whom a severe flare was evaluated solely based on an adjustment of the therapy.
b: Calculation of the IQWiG
c: Sensitivity analysis 2 corresponds to sensitivity analysis 1 but additionally without considering those patients in whom an increase of the SELENA-SLEDAI to > 12 was evaluated as a flare (according to the original planning in the PLUTO study).
d: For patients who continued the study in Part B or C, only AEs that occurred up to 4 weeks after the last dose of study medication were considered; for patients who stopped the study after Part A, only AEs that occurred up to 8 weeks after the last dose were considered.

Abbreviations:
HR: hazard ratio; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; n.a.: not achieved; RCT: randomised controlled trial; RR: relative risk; SELENA: Safety of Estrogens in Lupus Erythematosus – National Assessment; SFI: SELENA-SLEDAI SLE Flare Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SOC: System Organ Class; SAE: Serious Adverse Event; AE: Adverse Event; vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment.
Morbidity	n.a.	No assessable data were submitted for the benefit assessment.
Health-related quality of life	n.a.	No assessable data were submitted for the benefit assessment.
Side effects	↑	Advantage for the SAEs

Explanations:
↑, ↓: statistically significant and relevant positive or negative effect with high or unclear risk of bias
↑↑, ↓↓: statistically significant and relevant positive or negative effect with low risk of bias
↔: no relevant difference
∅: no data available
n.a.: not assessable

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

Children and adolescents from 5 to 17 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy

approx. 30–550 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 Benlysta® (active ingredient: belimumab) at the following publicly accessible link (last access: 25 March 2020):

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

Treatment with belimumab should only be initiated and monitored by specialists who are experienced in the treatment of patients with SLE.

4. Treatment costs

Annual treatment costs:

Children and adolescents from 5 to 17 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Belimumab	€ 4.520,62 – 14,034.67
patient-individual standard therapy	
Azathioprine	different for each individual patient
Hydroxychloroquine	€ 90.74 – 181.48
Chloroquine[2]	€ 49.72
Prednisone	different for each individual patient
Prednisolone	different for each individual patient
Ibuprofen	different for each individual patient
Appropriate comparator therapy:	
Azathioprine	different for each individual patient

[2] Available only as import

Designation of the therapy	Annual treatment costs/patient
Hydroxychloroquine	€ 90.74 – 181.48
Chloroquine[2]	€ 49.72
Prednisone	different for each individual patient
Prednisolone	different for each individual patient
Ibuprofen	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2020

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Belimumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	13	€ 923

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 14 May 2020.

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

Berlin, 14 May 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken