Resolution
by the Federal Joint Committee
on an amendment to the Pharmaceutical Directive (AM-RL):
Appendix XII – Resolutions on the benefit assessment of pharmaceuticals with new active ingredients, in accordance with the German Social Code, Book Five (SGB V), section 35a
Belimumab

from 2 August 2012

In its session on 2 August 2012, the Federal Joint Committee resolved to amend the Pharmaceutical Directive (AM-RL), version published 18 December 2008/22 January 2009 (Federal Gazette, number 49a of 31 March 2009), last amended on 21 June 2012 (Federal Gazette, AT 10 August 2012 B5), as follows:

I.

Appendix XII shall be amended in alphabetical order to include the active ingredient belimumab:

Belimumab

Therapeutic indication:

Benlysta® is indicated as an add-on therapy in adult patients 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.

1. Additional benefit of the pharmaceutical over appropriate comparator

Appropriate comparator: optimized standard therapy

(chloroquine/hydroxychloroquine, non-steroid anti-inflammatory drugs (NSAIDs), glucocorticoids, azathioprine, possibly cyclophosphamide) under consideration of authorized dosages and authorization status of each active ingredient.

Extent and probability of additional benefit over optimized standard therapy:

Indication of a considerable additional benefit

Study results[1] (meta-analysis of studies BLISS-52 and BLISS-76)[2] according to endpoints for the population "adult patients 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, with medication authorized in Germany as accompanying medication".

	Effect size [95% CI]/ Event rates [absolute risk reduction (ARR)][3] Belimumab 10mg/kg/body weight + optimized standard therapy vs. placebo + optimized standard therapy	p-value
SRI (SLE responder index in week 52)[4]	OR 2.365 [1.559; 3.589] 52.6% vs. 35.0% ARR = 17.2%	p = 0.0001
SRI individual components		
SELENA-SLEDAI (reduction ≥ 4)	OR 2.329 [1.533; 3.538] 53.4% vs. 36.9% ARR = 16.5%	p = 0.0001
BILAG (no new 1A/2B)	OR 1.943 [1.255; 3.010] 77.6% vs. 65.0% ARR = 12.6%	p = 0.0029
PGA (no increase > 0.3)	OR 1.906 [1.253; 2.899] 74.6% vs. 61.1% ARR = 13.5%	p = 0.0026

	Effect size [95% CI]/ Event rates [absolute risk reduction (ARR)][3] Belimumab 10mg/kg/body weight + optimized standard therapy vs. placebo + optimized standard therapy	p-value
Flares (SLE flare index, SFI)		
SFI: time until first severe flare	HR: 0.592 [0.395; 0.889]	p = 0.0114
SFI: number of severe flares per patient-year	Incidence ratio 0.540 [0.367; 0.796]	p = 0.0018
Flares (BILAG)		
BILAG: time until first flare (1A/2B)	HR: 0.600 [0.293; 1.228]	p = 0.1621
BILAG: flare per patient-year	Incidence ratio 0.556 [0.361; 0.855]	p = 0.0075
Fatigue	No applicable data available	
Prednisolone dosage change[5] (the figure 7.5 mg/day refers to the equivalent prednisolone dosage)		
Reduction by ≥ 25% to ≤ 7.5 mg/day (week 40 – 52)	OR: 1.328 [0.651; 2.710] 16.6% vs. 12.4%	p = 0.4354
Reduction to ≤ 7.5 mg/day in week 52	OR: 1.423 [0.760; 2.664] 22.5% vs. 16.5%	p = 0.2705
Increase to > 7.5 mg/day in week 52	OR: 0.670 [0.230; 1.950] 28.4% vs. 37.8%	p = 0.4620
Health-related quality of life		
SF-36: physical health (PCS) (week 52)	Hedges' g: 0.167 [-0.022; 0.356]	p = 0.0840
SF-36: mental health (MCS) (week 52)	Hedges' g: 0.186 [-0.146; 0.517]	p = 0.2721
EQ-5D Aggregate score (week 52)	Hedges' g: 0.127 [-0.091; 0.345]	p = 0.2524
Side effects		
Adverse events (AE)	OR: 1.509 [0.728; 3.130] 94.0% vs. 91.1%	p = 0.2690
Serious AE	OR: 1.314 [0.788; 2.192] 18.5% vs. 14.8%	p = 0.2949
Discontinuation of study medication due to AE	OR: 0.769 [0.303; 1.507] 7.8% vs. 9.9%	p = 0.4445
Death	OR: 1.76 [0.16; 19.65] 0.9% vs. 0.5%	p = 0.6458
Infections	OR: 1.198 [0.800; 1.792] 69.0% vs. 65.0%	p = 0.3804
Serious infections	OR: 0.802 [0.366; 1.755] 5.6% vs. 6.9%	p = 0.5801

[1] Data from the Benlysta®dossier, module 4

[2] Number of patients in the analysis
BLISS 52 (HGS 1006-C1057): Verum: 126/belimumab: 144
BLISS 76 (HGS 1006-C1056): Verum: 77/belimumab: 88

[3] Own calculation, ARR figures shown for significant differences only

[4] Compiled endpoint (primary endpoint):
1. SELENA SLEDAI score (reduction by ≥ 4 points from baseline value)
2. No worsening of PGA score (increase of 0.30 points over baseline value)
3. No new BILAG A organ systems affected, or fewer than 2 new BILAG B organ systems affected compared to baseline value in week 52

[5] In this analysis, patients grouped as "therapy failed" in the study protocol due to the unauthorized use of pharmaceuticals as accompanying medication (including unauthorized increase in steroid dosages) are not included.

2. Number of patients and criteria for defining patients eligible for treatment

   Target population: approx. 7,000

3. Requirements for quality-assured administration

   The specifications outlined in the product information are to be followed.

   The European Medicines Agency (EMA), the European regulatory authority, provides the product information for Benlysta® (active ingredient: Belimumab) at the following public link:

   http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002015/WC500110150.pdf

   Last accessed: 24 July 2012

4. Costs of treatment

   Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per year[1]	Duration of treatment each treatment (days)	Treatment days per patient per year
Pharmaceutical evaluated				
Belimumab	Year 1: on days 0, 14, 28, and then every 4 weeks	15 treatments	1	15
	from year 2: every 4 weeks	13 treatments	1	13
Appropriate comparator[1]				
Glucocorticoids e.g. prednisolone	ongoing (daily)	ongoing	365	365
NSAIDs e.g. indometacin	ongoing (daily)	ongoing	365	365
Hydroxychloroquine	ongoing (daily)	ongoing	365	365
Chloroquine	ongoing (daily)	ongoing	365	365
Azathioprine	ongoing (daily)	ongoing	365	365

[1] The appropriate comparator is an optimized standard therapy. It is patient-individualized, and can comprise one or more of the active ingredients listed.

Consumption:

Description of therapy	Strength	Number/amount per pack	Average annual consumption
Pharmaceutical evaluated			
Belimumab	10 mg/kg body weight	400 mg[1]	30 packs[2]
			26 packs[2]
Appropriate comparator			
Glucocorticoids e.g. prednisolone	5 mg	100 tablets[1] (5 mg each)	365 tablets
	100 mg [2 x 50 mg]	50 tablets[1] (50 mg each)	730 tablets
NSAIDs e.g. indometacin	50 mg – 150 mg [50 mg – 3 x 50 mg]	100 tablets[1] (50 mg each)	365 – 1,095 tablets
Hydroxychloroquine	310 mg [2 x 155 mg]	100 coated tablets[1] (155 mg each)	730 tablets
Chloroquine	≤ 2.5 mg/kg body weight	100 tablets[1] (155 mg each)	365 – 438 tablets[2]
Azathioprine	< 1 – 3 mg/kg body weight	100 coated tablets[1] (100 mg each)	273.75 – 821.25 tablets[2]

[1] Largest pack or pack with greatest strength
[2] 75 kg body weight

Costs:

Cost of pharmaceutical:

Description of therapy	Cost (pharmacy retail price)	Cost after legally mandated rebates
Pharmaceutical evaluated		
Belimumab	€948.30/pack	€827.57 (€120.73[1])
Belimumab is authorized as an add-on therapy. The costs of the appropriate comparator (optimized standard therapy) must be calculated as additional necessary pharmaceuticals.		
Appropriate comparator		
Glucocorticoids e.g. prednisolone	€14.61[2]/100 tablets (5 mg each)	€12.23 (€2.38[1])
	€30.62[2]/50 tablets (50 mg each)	€26.98 (€3.64[1])
NSAIDs e.g. indometacin	€17.39[2]/100 tablets	€14.79 (€2.60[1])
Hydroxychloroquine	€28.49[2]/100 coated tablets	€26.44 (€2.05[1])
Chloroquine	€28.49[2]/100 tablets	€24.23 (€4.26[1])
Azathioprine	€65,97[2]/100 coated tablets	€59.53 (€6.44[1])

[1] Rebates in accordance with SGB V, sections 130 and 130a
[2] Reference price

"Lauer-Taxe", effective 1 July 2012

Costs for additional, necessary statutory health insurance (SHI) benefits:

Description of therapy	Additional necessary SHI expense items			
	Description	Frequency	Number per patient/year	Cost per unit
Pharmaceutical evaluated				
Belimumab	none[1]			
Appropriate comparator				
none				

[1] According to the product information, a premedication consisting of an antihistamine with or without an antipyretic can be administered before the Benlysta® infusion.

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Belimumab	€24,827.10 (1st year of treatment) (plus costs for the appropriate comparator)
	€21,516.82 (2nd and following years of treatment) (plus costs for the appropriate comparator)
Appropriate comparator	€44.64 – €1,237.76[1]

[1] €44.64 = prednisolone 5mg/d
€1,237.76 = prednisolone 100mg/d; hydroxychloroquine 310mg/d; azathioprine 3 mg/kg/body weight/d; indometacin 150mg/d

II.

This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 2 August 2012.

The justification for this resolution will be published on the website of the Federal Joint Committee at www.g-ba.de.

Berlin, 2 August 2012

The Federal Joint Committee
in accordance with SGB V,
section 91

The Chair
Hecken