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 Ibrutinib (New Therapeutic Indication: Chronic Lymphatic Leukaemia, First-Line, in Combination with Obinutuzumab)

of 20 February 2020

At its session on 20 February 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 ibrutinib in accordance with the resolution of 16 March 2017:

Ibrutinib

Resolution of: 20 February 2020
Entry into force on: 20 February 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 2 August 2019):

IMBRUVICA as a single agent or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1)

Note:

The G-BA has already passed a resolution on the additional benefit of ibrutinib as a single agent for the treatment of adult patients with previously untreated CLL on 15 December 2016 and 21 July 2016.

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

a) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Appropriate comparator therapy:

- Fludarabine in combination with cyclophosphamide and rituximab (FCR)

Extent and probability of the additional benefit of ibrutinib in combination with obinutuzumab compared with the appropriate comparator therapy:

An additional benefit is not proven.

b) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Appropriate comparator therapy:

- Bendamustine in combination with rituximab

or

- Chlorambucil in combination with rituximab or obinutuzumab

Extent and probability of the additional benefit of ibrutinib in combination with obinutuzumab compared with chlorambucil in combination with obinutuzumab:

Hint for a minor additional benefit.

c) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

Appropriate comparator therapy:

- Ibrutinib

Extent and probability of the additional benefit of ibrutinib in combination with obinutuzumab compared with the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

There is no data that would allow for the assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.
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		

b) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

ILLUMINATE study: Ibrutinib + obinutuzumab **vs** chlorambucil + obinutuzumab

Relevant sub-population: Patients who are not eligible for FCR therapy

[1] Data from the dossier evaluation of the IQWiG (A19-77) unless otherwise indicated.

Mortality

Endpoint	Ibrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Intervention vs Control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95 % CI] p value[a] Absolute difference (AD)[b]
Overall survival					
	73	n.a. *15 (20.5)*	72	n.a. *12 (16.7)*	1.21 [0.55; 2.68] 0.638

Morbidity

Endpoint							
Progression-free survival (PFS) assessed by IRC[c]							
	73	n.a. [n.a.; n.a.] *17 (23.3)*		72	22.11 [18.43; 27.70] *43 (59.7)*		0.26 [0.15; 0.47] < 0.0001 AD = n.c.
Health status (EQ-5D VAS)							
	N[d]	Values at start of study MV (SD)	Change at evaluation time[e] MV[f] (SE)	N[d]	Values at start of study MV (SD)	Change at evaluation time[e] MV[f] (SE)	
Health status (EQ-5D VAS)[g]	70	75.78 (14.76)	1.89 (1.29)	65	70.33 (18.00)	5.62 (1.37)	-3.73 [-7.43; -0.03]; 0.048 Hedges' g: -0.34 [-0.68; 0.00]

Health-related quality of life

Endpoint
Not collected.

Side effects

Endpoint	Ibrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Intervention vs Control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value[a] Absolute difference (AD)[b]
Adverse events (AEs, presented additionally)[h]					
	73	0.26 [0.13; 0.39] *72 (98.6)*	71	0.03 [n.c.] *69 (97.2)*	-
Serious adverse events (SAEs)[h]					
Total	73	18.79 [11.24; n.c.] *42 (57.5)*	71	10.61 [n.c.] *27 (38.0)*	0.52 [0.28; 0.97]; 0.040
Sub-groups according to sex					
Women	29	27.6 [15.0; n.c.] *14 (48.3)*	22	n.a. [3.7; n.c.] *10 (45.5)*	0.24 [0.07; 0.87]; 0.029
Men	44	13.6 [6.9; 42.3] *28 (63.6)*	49	10.6 [n.c.] *17 (34.7)*	0.69 [0.32; 1.47]; 0.335
					Interaction: 0.031
Severe adverse events (CTCAE grade ≥ 3)[h]					
	73	6.24 [3.22; 7.59] *58 (79.5)*	71	2.79 [0.95; 4.04] *55 (77.5)*	0.48 [0.31; 0.73]; < 0.001
Sub-groups according to sex					
Women	29	7.59 [1.9; 24.5] *23 (79.3)*	22	1.41 [0.13; 3.71] *20 (90.9)*	0.18 [0.07; 0.44]; < 0.001
Men	44	3.99 [2.0; 7.4] *35 (79.5)*	49	2.79 [1.0; 4.6] *35 (71.4)*	0.65 [0.38; 1.10]; 0.108
					Interaction: 0.027
Discontinuation due to AEs (≥ 1 active ingredient)[h]					
	73	n.a. *19 (26.0)*	71	n.a. *10 (14.1)*	0.51 [0.17; 1.50]; 0.220

Specific AEs[h]					
Reaction associated with an infusion (PT, AEs)[h]					
	73	n.a. *18 (24.7)*	71	1.02 [0.03; n.c.] *37 (52.1)*	0.43 [0.24; 0.76]; 0.004
Severe haemorrhages (modified SMQ[i])[h]					
	73	n.a. *1 (1.4)*	71	n.a. *0 (0)*	n.c.
Cardiac disorders (SOC, AEs)[h]					
	73	n.a. [22.64; n.c.] *30 (41.1)*	71	n.a. *4 (5.6)*	5.13 [1.75; 15.06]; 0.003
Severe cardiac disorders (SOC, CTCAE grade ≥ 3)[h]					
	73	n.a. *10 (13.7)*	71	n.a. *0 (0)*	n.c. 0.124[j]
Infections and infestations (SOC, AEs)[h]					
	73	7.46 [4.07; 12.58] *53 (72.6)*	71	27.40 [5.19; 27.40] *28 (39.4)*	1.19 [0.72; 1.98]; 0.498
Severe neutropoenia (PT, CTCAE grade ≥ 3)[h]					
	73	n.a. [14.85; n.c.] *27 (37.0)*	71	5.65 [4.04; n.c.] *35 (49.3)*	0.44 [0.25; 0.76]; 0.003
Sub-groups according to sex					
Women	29	n.a. *7 (24.1)*	22	4.63 [3.68; n.c.] *13 (59.1)*	0.09 [0.02; 0.42]; 0.002
Men	44	n.a. [5.59; n.c.] *20 (45.5)*	49	n.a. [4.21; n.c.] *22 (44.9)*	0.66 [0.34; 1.28]; 0.219
					Interaction: 0.018
Nausea (PT, AEs)[h]					
	73	n.a. [n.c.] *9 (12.3)*	71	n.a. [n.c.] *18 (25.4)*	0.25 [0.10; 0.64]; 0.004
Skin and subcutaneous tissue disorders (SOC, AEs)[h]					
	73	12.94 [5.52; n.c.] *38 (52.1)*	71	n.a. [n.c.] *15 (21.1)*	2.00 [1.07; 3.76]; 0.031

[a] Cox proportional-hazards model, stratified according to ECOG PS and cytogenetics
[b] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[c] Data from the dossier of the pharmaceutical company; first data cut-off
[d] Number of patients who were taken into account in the evaluation for the calculation of the effect estimator (i.e. had values at baseline and at least one post baseline); values at baseline may be based on other patient numbers.
[e] End of observation upon disease progression or at completion of trial (median period of observation 40.1 months vs 21.0 months)
[f] MMRM with treatment, values at visits and baseline as fixed effects, patient as random effect
[g] A positive change over the course of the study indicates an improvement; a positive mean difference indicates an advantage for the trial intervention.
[h] Observation until 30 days after the last study medication dose (median observation period 40.5 vs 6.1 months)
[i] Modified SMQ "haemorrhage terms": includes all serious or severe (CTCAE grade ≥ 3) haemorrhages and central nervous system haemorrhages of any degree of severity; events based on laboratory values are not included
[j] p value: Log rank test

Acronyms used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC PS: Eastern Cooperative Oncology Performance Status; EQ-5D: European Quality of Life – 5 Dimensions; FCR: fludarabine in combination with cyclophosphamide and rituximab; HR = hazard ratio; IRC = Independent Review Committee; CI = confidence interval; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; MMRM: mixed model with repeated measurements; MV: mean value; N = number of patients assessed; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT: preferred term; SMQ: standardised MedDRA queries; SD standard deviation; SE: standard error; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment
Morbidity	↔	No difference relevant for the benefit assessment
Health-related quality of life	∅	No data available.
Side effects	↑	Advantages in the endpoints SAEs and severe AEs (CTCAE grade ≥ 3)

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

c) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

There is no suitable data that would allow for the assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.
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

a) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Approx. 1810 patients

b) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Approx. 810 patients

c) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

Approx. 470 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 Imbruvica® (active ingredient: ibrutinib) at the following publicly accessible link (last access: 2 January 2020):

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

Treatment with ibrutinib in combination with obinutuzumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with chronic lymphocytic leukaemia.

4. Treatment costs

Annual treatment costs:

a) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ibrutinib	€ 77,914.20
Obinutuzumab	€ 27,900.56
Additionally required SHI services	€ 144.48
Total:	€ 105,959.24
Appropriate comparator therapy:	
Fludarabine + cyclophosphamide + rituximab (FCR)	
Fludarabine	€ 1,892.40
Cyclophosphamide	€ 213.69
Rituximab	€ 19,800.06
Additionally required SHI services	€ 57.40
Total:	€ 21,963.55

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

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Obinutuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	Cycle 1: 4 Cycle 2–6: 1	9	€ 639
Fludarabine	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 81	3	18	€ 1,458
Cyclophosphamide	Surcharge for the preparation of a	€ 81	3	18	€ 1,458

	parenteral solution containing cytostatic agents				
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426

b) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ibrutinib	€ 77,914.20
Obinutuzumab	€ 27,900.56
Additionally required SHI services	€ 144.48
Total:	€ 105,959.24
Appropriate comparator therapy:	
Bendamustine + rituximab (BR)	
Bendamustine	€ 5,332.80
Rituximab	€ 19,800.06
Additionally required SHI services	€ 57.40
Total:	€ 25,190.26
Chlorambucil + rituximab (ClbR)	
Chlorambucil	€ 339.75
Rituximab	€ 19,800.06
Additionally required SHI services	€ 57.40
Total:	€ 20,197.21
Chlorambucil + obinutuzumab	
Chlorambucil	€ 339.75
Obinutuzumab	€ 27,900.56
Additionally required SHI services	€ 144.48
Total:	€ 28,384.79

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

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Obinutuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	Cycle 1: 4 Cycle 2–6: 1	9	€ 639
Bendamustine	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 81	2	12	€ 972
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426

c) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ibrutinib	€ 77,914.20
Obinutuzumab	€ 27,900.56
Additionally required SHI services	€ 144.48
Total:	€ 105,959.24
Appropriate comparator therapy:	
Ibrutinib	
Ibrutinib	€ 77,914.20

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

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Obinutuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal	€ 71	Cycle 1: 4 Cycle 2–6: 1	9	€ 639

	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 20 February 2020.

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

Berlin, 20 February 2020

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

Prof. Hecken