Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee on an amendment to 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 Lymphoblastic Leukaemia, First-line, in Combination with Rituximab)

of 1 April 2021

At its session on 1 April 2021 the Federal Joint Committee (G-BA) resolved to amend the 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 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 20 February 2020:

Ibrutinib

Resolution of: 1 April 2021
Entry into force on: 1 April 2021
BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 28 August 2020:

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

Therapeutic indication of the resolution (resolution from 1 April 2021):

IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)

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

a) Adult patients with previously untreated chronic lymphocytic leukaemia, 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 rituximab compared to fludarabine in combination with cyclophosphamide and rituximab (FCR):

Hint for a considerable additional benefit

b) Adult patients with previously untreated chronic lymphocytic leukaemia, not eligible for therapy with 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 rituximab compared to the appropriate comparator therapy:

An additional benefit is not proven.

c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons

Appropriate comparator therapy:

– Ibrutinib

Extent and probability of the additional benefit of ibrutinib in combination with rituximab compared to 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, eligible for a therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	↔	no statistically significant difference
Health-related quality of life	∅	No data available.
Side effects	↑	Mainly advantages with severe AE, discontinuation because of AE and specific AE

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

ECOG-E1912 study: Ibrutinib + rituximab **vs** fludarabine + cyclophosphamide + rituximab

Relevant sub-population: Patients eligible for a FCR therapy

Mortality

Endpoint	Ibrutinib + rituximab		FCR		Ibrutinib + rituximab vs FCR
	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 (%)*	[95 %- CI] p value Absolute difference (AD)[a]
Overall survival					
Main analysis	141	n.a.	65	n.a.	n.a.

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A20-88) unless otherwise indicated.

1. Data cut-off (17.07.2018)		*0 (0)*		*6 (9.2)*	< 0.001 AD: n.c.
Main analysis 2. Data cut-off (02.08.2019)	141	n.a. *0 (0)*	65	n.a. *7 (10.8)*	n.a. < 0.001 AD: n.c.
Sensitivity analysis 2. Data cut-off[b]	141	n.a. *1 (0.7)*	65	n.a. *7 (10.8)*	0.06 [0.01; 0.48] < 0.001 AD: n.c.

Morbidity

Progression-free survival (PFS) [c]							
	141	n.a. [n.a.; n.a.] *17 (12.1)*		65	57.3. [43,99; n.a.] *23 (35.4)*		0.25 [0.14; 0.48] < 0.0001 AD: n.c.
	N	Values at the start of the study MV (SD)	Mean change in the course of study MV (SE)	N	Values at the start of the study MV (SD)	Mean change in the course of study MV (SE)	MD [95 %- CI] p value
FACT-Leu TOI							
FACT-Leu TOI[d]	139	93.2 (19.0)	6.0 (1.0)	64	93.5 (17.4)	8.1 (1.5)	-2.04 [-5.58; 1.50] 0.258
PWB	140	22.8 (5.4)	0.4 (0.3)	65	23.5 (4.2)	0.5 (0.4)	-0.08 [-1.11; 0.95]
FWB	140	20.6 (5.7)	1.1 (0.3)	65	20.3 (5.5)	1.8 (0.4)	-0.74 [-1.77; 0.30]
Leu	139	49.6 (9.9)	4.5 (0.5)	64	49.8 (9.5)	5.9 (0.8)	-1.41 [-3.27; 0.46]

Health-related quality of life

Not collected

Side effects

Endpoint	Ibrutinib + rituximab		FCR		Ibrutinib + rituximab vs FCR
	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 Absolute difference (AD)[a]
Total adverse events (AE) (presented additionally)					
	141	1.0 [n. c; n. c.] *141 (100.0)*	65	1.0 [n. c; n. c.] *65 (100.0)*	–
Serious adverse events (SAE)					
No results available					
Severe adverse events (CTCAE grade ≥ 3)					
	141	1.9 [1.0; 1.9] *126 (89.4)*	65	1.0 [1.0; 1.9] *59 (90.8)*	0.71 [0.52; 0.97] 0.035 AD: +0.9 months
Discontinuation because of AE (≥ 1 component)					
	141	n.a. *15 (10.6)*	65	n.a. *8 (12.3)*	0.29 [0.10; 0.86] 0.025 AD: n.c.
Specific adverse events					
Haemorrhages					
severe haemorrhages (SMQ haemorrhage terms [excl. laboratory terms][f]. severe AE[e])[g]	141	n.a. *1 (0.7 %)*	65	n.a. *0 (0)*	n.c.
haemorrhages (SMQ haemorrhage terms [excl. laboratory terms][f]. AE)[g]	141	37.7 *66 (46.8)*	65	n.a. *6 (9.2)*	3.46 [1.47; 8.12] 0.0044 AD: n.c.
Contusion (PT. AE)	141	n.a. *41 (29.1)*	65	n.a. *3 (4.6)*	4.47 [1.36; 14.70] 0.014 AD: n.c.
Infections and infestations (SOC. AE)	141	21.2 [12.9; 26.7] *90 (63.8)*	65	n. a. [5.6; n. c.] *24 (36.9)*	0.78 [0.48; 1.28] 0.323

Upper respiratory tract infection (PT. AE)	141	n. a. [40.5; n. c.] *50 (35.5)*	65	n.a. *17 (26.2)*	0.31 [0.15; 0.63] 0.001 AD: n.c.
Heart diseases (SOC. severe AE[e])	141	n.a. *11 (7.8)*	65	n.a. *0 (0)*	n.a. 0.266
Nausea (PT. AE)	141	37.8 [12.9; n. a.] *69 (48.9)*	65	1.0 [1.0; 2.8] *45 (69.2)*	0.42 [0.28; 0.62] < 0.001 AD: + 36.8 months
Constipation (PT. AE)	141	n.a. *29 (20.6)*	65	n.a. *22 (33.8)*	0.33 [0.18; 0.61] < 0.001 AD: n.c.
Vomiting (PT. AE)	141	n.a. *28 (19.9)*	65	n.a. *20 (30.8)*	0.30 [0.15; 0.58] < 0.001 AD: n.c.
Decreased appetite (PT. AE)	141	n.a. *21 (14.9)*	65	n.a. *17 (26.2)*	0.37 [0.18; 0.74] 0.005 AD: n.c.
Pollakiuria (PT. AE)	141	n.a. *8 (5.7)*	65	n.a. *8 (12.3)*	0.18 [0.05; 0.63] 0.007 AD: n.c.
Lymphopenia (PT. severe AE[e])	141	n.a. *12 (8.5)*	65	2.8 [1.9; 3.7] *49 (75.4)*	0.03 [0.01; 0.08] < 0.001 AD: n.c.
Leukopenia (PT. severe AE[e])	141	n.a. *11 (7.8)*	65	n. a. [5.6; n. c.] *25 (38.5)*	0.06 [0.02; 0.17] < 0.001 AD: n.c.
febrile neutropenia (PT. severe AE[e])	141	n.a. *1 (0.7)*	65	n.a. *8 (12.3)*	0.05 [0.01; 0.41] 0.005 AD: n.c.
Thrombocytopenia (PT. severe AE[e])	141	n.a. *2 (1.4)*	65	n.a. *4 (6.2)*	0.11 [0.01; 0.97] 0.047 AD: n.c.
Leukocytosis (PT. severe AE[e])	141	n.a. *21 (14.9)*	65	n.a. *1 (1.5)*	8.02 [1.07; 60.28] 0.043 AD: n.c.
Lymphocytosis (PT. severe AEs[e])	141	1.9 [1.9; n. a.] *78 (55.3)*	65	n.a. *17 (26.2)*	2.16 [1.28; 3.66] 0.004 AD: n.c.
Hyperglycemia (PT. severe AEs[d])	141	n.a. *6 (4.3)*	65	n.a. *4 (6.2)*	0.15 [0.02; 0.96] 0.045

					AD: n.c.

[A] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Information from the dossier of the pharmaceutical company; 2nd data cut-off
[c] For calculating the effect estimates and confidence intervals one event was imputed in the intervention arm.
[d] Higher (increasing) values mean better well-being; positive effects (intervention minus control) mean an advantage for the intervention.
[E] operationalised as CTCAE grade ≥ 3
[f] "Excluding laboratory terms" means that the SMQ does not contain PTs resulting from laboratory tests.
[g] Data subsequently submitted from the pU of the written statement procedure

Abbreviations used:
AD = Absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; FACT-Leu: Functional Assessment of Cancer Therapy – Leukaemia; FCR = FCR: Fludarabin + cyclophosphamide + rituximab; FWB: Functional well-being; HR = Hazard ratio; n.d. = no data available; CI = confidencial interval; MedDRA = Medical Dictionary for Regulatory Activities; FWB: Functional well-being; MD: mean difference; MV: Mean value; N = number of patients evaluated; n= number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PWB: Physical well-being; PT = Preferred term; SD: Standard deviation; SE: Starndard error; SMQ: Standardised MedDRA Query; SOC: system organ class; vs. versus; TOI: Trial Outcome Index

b) Adult patients with previously untreated chronic lymphocytic leukaemia. not eligible for a therapy with FCR

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 effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons

Summary of results for relevant clinical endpoints

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Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

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

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

approx. 1810 patients

b) Adult patients with previously untreated chronic lymphocytic leukaemia, not eligible for therapy with FCR

approx. 810 patients

c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to 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: 29 January 2021):
https://www.ema.europa.eu/documents/product-information/imbruvica-epar-product-information_de.pdf

Treatment with ibrutinib combined with rituximab should only be initiated and monitored by specialists in internal medicine, haematology and oncology 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, 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	€ 75.227.15
Rituximab	€ 19.800.06
additionally required SHI services	€ 68.95
Total:	€ 95.096.16
Appropriate comparator therapy:	
Fludarabin + cyclophosphamide + rituximab (FCR)	
Fludarabine	€ 1.892.40
Cyclophosphamide	€ 213.69
Rituximab	€ 19.800.06
additionally required SHI services	€ 57.55
Total:	€ 21.963.70

Costs after deduction of statutory rebates (LAUER-TAXE®. as last revised: 15 March 2021)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	18	€ 1458
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	18	€ 1458
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, not eligible for therapy with FCR

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ibrutinib	€ 75.227.15
Rituximab	€ 19.800.06
additionally required SHI services	€ 68.95
Total:	€ 95.096.16
Appropriate comparator therapy:	
Bendamustine + rituximab (BR)	
Bendamustine	€ 5.261.55
Rituximab	€ 19.800.06
additionally required SHI services	€ 57.55
Total:	€ 25.119.16
Chlorambucil + rituximab (ClbR)	
Chlorambucil	€ 165.70
Rituximab	€ 19.800.06
additionally required SHI services	€ 57.55
Total:	€ 20.023.31
Chlorambucil + obinutuzumab	
Chlorambucil	€ 165.70
Obinutuzumab	€ 27.900.56
additionally required SHI services	€ 144.68
Total:	€ 28.210.94

Costs after deduction of statutory rebates (LAUER-TAXE®. as last revised: 15 March 2021)

Other SHI services:

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

c) <u>Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons.</u>

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ibrutinib	€ 75.227.15
Rituximab	€ 19.800.06
additionally required SHI services	€ 68.95
Total:	€ 95.096.16
Appropriate comparator therapy:	
Ibrutinib	
Ibrutinib	€ 75.227.15
additionally required SHI services	€ 11.40
Total:	€ 75.238.55

Costs after deduction of statutory rebates (LAUER-TAXE®. as last revised: 15 March 2021)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426

II. Entry into force

1. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 1 April 2021.

2. The period of validity of the resolution is limited in accordance with the following regulation:

The respective findings in numbers 1. 2. 3 and 4 regarding the patient group a) "Adult patients with previously untreated chronic lymphocytic leukaemia, eligible for a therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)" are limited to the 1 April 2024.

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

Berlin. 1 April 2021

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

Prof. Hecken