Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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
Acalabrutinib (chronic lymphocytic leukaemia (CLL), as monotherapy, first-line)

of 3 June 2021

At its session on 3 June 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 on DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient acalabrutinib as follows:

Acalabrutinib

Resolution of: 3 June 2021
Entry into force on: 3 June 2021
BAnz AT TT. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 5 November 2020):

Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior treatment.

Therapeutic indication of the resolution (resolution of 3 June 2021):

Calquence as monotherapy 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 who do not have a 17p deletion or TP53-mutation and 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 acalabrutinib compared to the appropriate comparator therapy:

An additional benefit is not proven

b) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are not eligible for therapy with FCR

Appropriate comparator therapy:

- bendamustine in combination with rituximab

or

- chlorambucil in combination with rituximab or obinutuzumab

Extent and likelihood of additional benefit of acalabrutinib vs Chlorambucil in combination with obinutuzumab:

Hint for a minor additional benefit.

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 acalabrutinib 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 who do not have a 17p deletion or TP53-mutation and who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	∅	There are no evaluable data.
Morbidity	∅	There are no evaluable data.
Health-related quality of life	∅	There are no evaluable data.
Side effects	∅	There are no evaluable data.
Explanations: ↑: statistically significant and relevant positive effect with high or unclear risk of bias ↓: statistically significant and relevant negative effect with high or unclear risk of bias ↑↑: statistically significant and relevant positive effect with a low risk of bias ↓↓: statistically significant and relevant negative effect with data low risk of bias ↔: no relevant difference ∅: no data availablen.a.: not assessable		

[1] Data from the dossier assessment of the IQWiG (A20-103) and from the addendum (A21-52), unless otherwise indicated.

b) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are not eligible for therapy with FCR

Summary of results for relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑	Advantage in EQ-5D VAS
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↑	Advantages in the endpoints severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, as well as in detail for specific AEs

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

ELEVATE-TN study: Acalabrutinib vs. acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab

Study design: randomised, open, phase III

Relevant study arms: Acalabrutinib vs chlorambucil + obinutuzumab

Data cut-offs: 1. Data cut-off as of 8 February 2019: data cut-off as of 1 August 2019:

Mortality

Endpoint	Acalabrutinib		Chlorambucil + obinutuzumab		Acalabrutinib vs. chlorambucil + obinutuzumab
	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					
	103	n.a. *7 (6.8)*	95	n.a. *10 (10.5)*	0.63 [0.23; 1.65] 0,352

Morbidity

Endpoint	Acalabrutinib		Chlorambucil + obinutuzumab		Acalabrutinib vs. chlorambucil + obinutuzumab
	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]
Progression-free survival (PFS)[b]					
	103	n.a. *17 (16.5)*	95	23.2 [19.4; 27.8] *47 (49.5)*	0.25 [0.14; 0.42] <0,0001 AD: n.a.
Fatigue (FACIT-Fatigue)					
	103	n.a. *17 (16.5)*	95	n.a. *16 (16.8)*	0.84 [0.42; 1.68] 0.618
Disease-related symptomatology					
	no usable data available				
EORTC QLQ-C30 symptom scales					

Endpoint	Acalabrutinib		Chlorambucil + obinutuzumab		Acalabrutinib vs. chlorambucil + obinutuzumab
	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]
Fatigue	103	n. a. 24 (23.3)	95	n. a. 18 (18.9)	1.12 [0.61; 2.09] 0,721
Nausea and vomiting	103	n. a. 27 (26.2)	95	n. a. 21 (22.1)	1.00 [0.57; 1.80] 0.988
Pain	103	5.7 [3.0; 33.1] *50 (48.5)*	95	17.5 [6,7; n. c.] 33 (34.7)	1.37 [0.89; 2.15] 0,163
Dyspnoea	103	n. a. 21 (20.4)	95	n. a. 25 (26.3)	0.69 [0.38; 1.23] 0,203
Insomnia	103	n. a. 32 (31.1)	95	n. a. 28 (29.5)	0.98 [0.59; 1.64] 0,932
Loss of Appetite	103	n. a. 29 (28.3)	95	n. a. 19 (20.0)	1.23 [0.69; 2.23] 0,485
Constipation	103	n. a. 31 (30.1)	95	33,1 [12,0; n. c.] 30 (31.6)	0.80 [0.48; 1.32] 0,378
Diarrhoea	103	34,7 [34,7; n. c.] 24 (23.3)	95	n. a. 15 (15.8)	1.16 [0.61; 2.28] 0,656
Health status (EQ-5D VAS)					
	103	n. a. 16 (15.5)	95	n. a. 22 (23.2)	0.50 [0.25; 0.95] 0,032 AD: n.a.

Health-related quality of life

Endpoint	Acalabrutinib		Chlorambucil + obinutuzumab		Acalabrutinib vs. chlorambucil + obinutuzumab
	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]
EORTC QLQ-C30 – functional scales					
global health status	103	n. a. 28 (27.2)	95	28,1 [16,8; n. c.] 27 (28.4)	0.83 [0.49; 1.41] 0,484
physical functioning	103	n. a. 22 (21.4)	95	n. a. 12 (12.6)	1.51 [0.76; 3.14] 0,254
Role function	103	17,8 [4,1; n. c.] 43 (41.7)	95	16,8 [5,7; n. c.] 33 (34.7)	1.06 [0.68; 1.69] 0,797
Emotional function	103	n. a. 23 (22.3)	95	n. a. 24 (25.3)	0.73 [0.41; 1.31] 0,287
Cognitive function	103	22,4 [5,6; n. c.] 42 (40.8)	95	28,1 [11,0; n. c.] 30 (31.6)	1.17 [0.73; 1.88] 0,523
Social function	103	n. a. 38 (36.9)	95	16,6 [4,6; n. c.] 36 (37.9)	0.80 [0.51; 1.27] 0.349

Side effects

Endpoint	Acalabrutinib		Chlorambucil + obinutuzumab		Acalabrutinib vs. chlorambucil + obinutuzumab
	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]
Adverse events (presented additionally)					
	103	0.2 [0.1; 0.2] *101 (98.1)*	91	0.0 [n. c; n. c.] *90 (98.9)*	-
Serious adverse events (SAE)					
	103	n.a. *43 (41.7)*	91	n.a. *21 (23.1)*	0.78 [0.42; 1.44] 0,425
Severe adverse events (CTCAE grade ≥ 3)					
	103	14.6 [7.5; 25.9] *65 (63.1)*	91	0.5 [0.3; 1.1] *74 (81.3)*	0.26 [0.17; 0.38] < 0.001 AD: + 13.1
Discontinuation due to AEs (≥ 1 component)					
	103	n.a. *17 (16.5)*	91	n.a. *21 (23.1)*	0.32 [0.14; 0.70] 0,004 AD: n.a.
Specific adverse events					
Infections and infestations (SOC, AEs)	103	6.0 [3.0; 12.6] *79 (76.7)*	91	n. a. 44 (48.4)	1.14 [0.77; 1.71] 0,520
Cardiac disorders (SOC, AEs)	103	n. a. 22 (21.4)	91	n. a. 6 (6.6)	1.04 [0.35; 3.22] 0,945
Cardiac disorders (SOC, severe AEsc)	*103*	n. a. 12 (11.7)	*91*	n.a. 1 (1.1)	2.75 [0.37; 55.34] 0,358

Endpoint	Acalabrutinib		Chlorambucil + obinutuzumab		Acalabrutinib vs. chlorambucil + obinutuzumab
	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]
Bleeding (SMQ[d], severe AEs[c])	103	n. a. 3 (2.9)	91	n. a. 0 (0)	n. c.
Nausea (PT, AE)	103	n. a. 20 (19.4)	91	n. a. 32 (35.2)	0.34 [0.18; 0.62]; < 0.001 AD: n.a.
Blood and lymphatic system disorders (SOC, severe AEs[c])	103	n. a. 23 (22.3)	91	2.9 [1.1; 5.7] 54 (59.3)	0.24 [0.14; 0.39] < 0.001 AD: n.a.
Febrile neutropenia (PT, severe AEs[c])	103	n. a. 1 (1.0)	91	n. a. 6 (6.6)	0.14 [0.01; 0.84] 0,037 AD: n.a.
Metabolic and nutritional disorders (SOC, severe AEs[c])	103	n. a. 3 (2.9)	91	n. a. 20 (22.0)	0.10 [0.02; 0.31] < 0.001 AD: n.a.
Tumour lysis syndrome (PT, severe AEs[c])	103	n. a. 0 (0)	91	n. a. 11 (12.1)	n.a. < 0.001 AD: n.a.

Endpoint	Acalabrutinib		Chlorambucil + obinutuzumab		Acalabrutinib vs. chlorambucil + obinutuzumab
	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]

[a] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation

Data from the dossier acalabrutinib (Monotherapy) Module 4A of 01/12/2020

[c] operationalised as CTCAE grade ≥ 3

[d] The pharmaceutical company does not state in Module 4 A which events were considered for the endpoint "Bleeding". According to the information provided in the European Medicines Agency report, this is considered to be the SMQ "Bleeding".

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life Questionnaire - 5 Dimensions; FACIT = Functional Assessment of Chronic Illness Therapy; FCR = fludarabine + cyclophosphamide + rituximab; HR= hazard ratio; n. A. = not specified; CI = confidence interval; MedDRA = Medical Dictionary of Drug Regulatory Activities; n = number of patients with (at least 1) event; N = number of patients evaluated; n. b. = not calculable; n. a. = not achievable; PT = preferred term; pU = pharmaceutical company; QLQ-C30= Quality of Life Questionnaire - Core 30; RCT = randomised controlled trial; SMQ = standardised MedDRA query; SOC = system organ class; SUE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs. = versus

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>

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

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↓↓: statistically significant and relevant negative effect with data 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 who do not have a 17p deletion or TP53-mutation and who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

approx. 1550 to 1870

b) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are not eligible for therapy with FCR

approx. 840

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. 490 to 1070

3. Requirements for a quality-assured application

The requirements in the product information are to be considered. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Calquence (active ingredient: acalabrutinib) at the following publicly accessible link (last access: 11 March 2021):
https://www.ema.europa.eu/documents/product-information/calquence-epar-product-information_de.pdf

Initiation and monitoring of treatment with acalabrutinib should be performed only by specialists in internal medicine and haematology and oncology experienced in the therapy of patients with chronic lymphocytic leukaemia.

4. Treatment costs

Annual treatment costs:

a) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Acalabrutinib	€ 100,875.90
additionally required SHI services	€ 11.40
Total:	€ 100,887.30
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 May 2021).

Other SHI services:

Name of 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) <u>Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are not eligible for therapy with FCR</u>

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Acalabrutinib	€ 100,875.90
additionally required SHI services	€ 11.40
Total:	€ 100,887.30
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 May 2021).

Other SHI services:

Name of 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	€ 71	1	6	€ 426

	monoclonal antibodies				
Obinutuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	Cycle 1: 3 Cycle 2-6: 1	8	€ 568

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

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Acalabrutinib	€ 100,875.90
additionally required SHI services	€ 11.40
Total:	€ 100,887.30
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 May 2021).

II. The resolution will enter into force on the day of its publication on the internet on the G-BA website on 3 June 2021.

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

Berlin, 3 June 2021

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

Prof. Hecken