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), in combination with obinutuzumab, 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. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of acalabrutinib in accordance with the resolution of 3 June 2021:

Acalabrutinib in combination with obinutuzumab

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 in combination with obinutuzumab 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 in combination with obinutuzumab 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 probability of the additional benefit of acalabrutinib in combination with obinutuzumab compared to 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 in combination with obinutuzumab 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 orunclear risk of bias ↑↑: statistically significant and relevant positive effect with low risk of bias ↓↓: statistically significant and relevant negative effect low risk of bias ↔: no relevant difference ∅: no data available n.a.: not assessable		

[1] Data from the dossier assessment of the IQWiG (A20-104) and from the addendum (A21-53), unless otherwise indicated.

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

Summary of results for relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↓	Disadvantage in the symptom scale diarrhoea
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↑	Benefits in the endpoints severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, and in detail predominantly benefits in specific AEs
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 low risk of bias ↓↓: statistically significant and relevant negative effect 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 + obinutuzumab 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 + obinutuzumab		Chlorambucil + obinutuzumab		Acalabrutinib + obinutuzumab 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					
	99	n. a. 5 (5.1)	95	n.a. *10 (10.5)*	0,46 [0.14; 1.31] 0,151

Morbidity

Endpoint	Acalabrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Acalabrutinib + obinutuzumab 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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[b]					
	99	n.a. *11 (11.1)*	95	23.2 [19.4; 27.8] *47 (49.5)*	0,15 [0.08; 0.29] < 0.0001 AD: n.a.
Fatigue (FACIT-Fatigue)					
	99	n.a. *24 (24.2)*	95	n.a. *16 (16.8)*	1,18 [0.63; 2.26] 0,620
Disease-related symptomatology					
	no usable data available				
EORTC QLQ-C30 symptom scales					
Fatigue	99	n. a. 33 (33.3)	95	n. a. 18 (18.9)	1.54

Endpoint	Acalabrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Acalabrutinib + obinutuzumab 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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
					[0.87; 2.79] 0.143
Nausea and vomiting	99	n. a. 30 (30.3)	95	n. a. 21 (22.1)	1,15 [0.66; 2.04] 0.627
Pain	99	11.1 [3.7; n. c.] 48 (48.5)	95	17.5 [6.7; n. c.] 33 (34.7)	1.33 [0.86; 2.09] 0.207
Dyspnoea	99	n. a. 39 (39.4)	95	n. a. 25 (26.3)	1,36 [0.82; 2.27] 0,241
Insomnia	99	22,3 [4,8; n. c.] 41 (41.4)	95	n. a. 28 (29.5)	1,25 [0.78; 2.05] 0,366
Loss of Appetite	99	n. a. 28 (28.3)	95	n. a. 19 (20.0)	1,10 [0.62; 2.01] 0,747
Constipation	99	33,3 [22,1; n. c.] 34 (34.3)	95	33,1 [12,0; n. c.] 30 (31.6)	0,79 [0.48; 1.31] 0,359
Diarrhoea	99	16.7 [11.1; 33.3] *48 (48.5)*	95	n. a. 15 (15.8)	2,67 [1.53; 4.95] < 0.001 AD: n.a.
Health status (EQ-5D VAS)					
	99	n. a. 27 (27.3)	95	n. a. 22 (23.2)	0,85 [0.48; 1.52] 0,581

Health-related quality of life

Endpoint	Acalabrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Acalabrutinib + obinutuzumab 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	99	n. a. 37 (37.4)	95	28,1 [16,8; n. c.] 27 (28.4)	1,08 [0.66; 1.79] 0,775
physical functioning	99	n. a. 25 (25.3)	95	n. a. 12 (12.6)	1,69 [0.86; 3.49] 0,134
Role function	99	5,7 [2,8; n. c.] 49 (49.5)	95	16,8 [5,7; n. c.] 33 (34.7)	1.33 [0.86; 2.09] 0,208
Emotional function	99	33,2 [27,6; n. c.] 34 (34.3)	95	n. a. 24 (25.3)	1,01 [0.60; 1.73] 0,975
Cognitive function	99	16,7 [4,7; n. c.] 47 (47.5)	95	28,1 [11,0; n. c.] 30 (31.6)	1,30 [0.82; 2.07] 0,277
Social function	99	11,1 [3,1; n. c.] 48 (48.5)	95	16,6 [4,6; n. c.] 36 (37.9)	1,11 [0.72; 1.72] 0,650

Side effects

Endpoint	Acalabrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Acalabrutinib + obinutuzumab 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)					
	99	0.2 [0.1; 0.3] *96 (97.0)*	91	0.0 [n. c.; n. c.] *90 (98.9)*	-
Serious adverse events (SAE)					
	99	25,7 [14,8; n. c.] 53 (53.5)	91	n. a. 21 (23.1)	1,06 [0.60; 1.89] 0,848
Severe adverse events (CTCAE grade ≥ 3)					
	99	2.9 [1.8; 5.6] *77 (77.8)*	91	0.5 [0.3; 1.1] *74 (81.3)*	0,49 [0.34; 0.69] < 0.001 AD: + 2.4
Discontinuation due to AEs (≥ 1 component)					
	99	n. a. 16 (16.2)	91	n. a. 21 (23.1)	0,39 [0.18; 0.81] 0,011 AD: n.c.
Specific adverse events					
Infections and infestations (SOC, AEs)	99	8.2[4.6; 13.0] *72 (72.7)*	91	n. a. 44 (48.4)	0.92 [0.61; 1.39] 0,695
Cardiac disorders (SOC, AEs)	99	n. a. 21 (21.2)	91	n. a. 6 (6.6)	1.33 [0.48; 3.98] 0,584
Cardiac disorders (SOC, severe AEs[c])	99	n. a. 9 (9.1)	91	n. a. 1 (1.1)	2.68 [0.34; 54.07] 0,375

Endpoint	Acalabrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Acalabrutinib + obinutuzumab 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])	99	n. a. 2 (2.0)	91	n. a. 0 (0)	n. a. 0.346
Reaction associated with infusion (PT, AEs)	99	n. a. 15 (15.2)	91	n. a. 37 (40.7)	0.28 [0.15; 0.50] < 0.001 AD: n.a.
Nausea (PT, AE)	99	n. a. 18 (18.2)	91	n. a. 32 (35.2)	0.33 [0.17; 0.61] < 0.001 AD: n.a.
Nausea (PT, AE)	99	n. a. 36 (36.4)	91	n. a. 14 (15.4)	2.66 [1.46; 5.11] 0,002 AD: n.a.
Blood and lymphatic system disorders (SOC, severe AEs[c])	99	n. a. 47 (47.5)	91	2.9 [1.1; 5.7] *54 (59.3)*	0.49 [0.32; 0.74] < 0.001 AD: n.a.
Febrile neutropenia (PT, severe AEs[c])	99	n. a. 3 (3.0)	91	n. a. 6 (6.6)	0.15 [0.01; 0.85] 0,038 AD: n.a.
Metabolic and nutritional disorders (SOC, severe AEs[c])	99	n. a. 10 (10.1)	91	n. a. 20 (22.0)	0.26 [0.10; 0.60] 0,002 AD: n.a.
Tumour Lysis-syndrome (PT, severe AEs[c])	99	n. a. 1 (1.0)	91	n. a. 11 (12.1)	0.08 [0.00; 0.40] 0,002 AD: n.a.

Endpoint	Acalabrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Acalabrutinib + obinutuzumab 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] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

[b] Data from the dossier Acalabrutinib in combination with obinutuzumab module 4B dated 1.12.2020

[c] operationalised as CTCAE grade ≥ 3

[d] The pharmaceutical company does not state in Module 4 A which events were taken into account 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. c. = 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; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

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

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 orunclear risk of bias

↑↑: statistically significant and relevant positive effect with low risk of bias

↓↓: statistically significant and relevant negative effect 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 for whom therapy with FCR is not an option

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 in combination with obinutuzumab) 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 in combination with obinutuzumab should only be carried out by specialists in internal medicine and haematology and oncology experienced in the treatment of patients with chronic lymphocytic leukaemia.

4. Treatment costs

Annual treatment costs:

a) <u>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)</u>

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Acalabrutinib	€ 100,875.90
Obinutuzumab	€ 27,900.56
additionally required SHI services	€ 144.68
Total:	€ 128,921.14
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	€ 71	1	6	€ 426

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

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

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Acalabrutinib	€ 100,875.90
Obinutuzumab	€ 27,900.56
additionally required SHI services	€ 144.68
Total:	€ 128,921.14
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 monoclonal antibodies	€ 71	1	6	€ 426
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
Obinutuzumab	€ 27,900.56
additionally required SHI services	€ 144.68
Total:	€ 128,921.14
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).

Other SHI services:

Name of 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: 3 Cycle 2-6: 1	8	€ 568

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