Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-L):

Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V:

Acalabrutinib (Chronic lymphocytic leukaemia, after at least 1 previous treatment)

of 5 August 2021

At its session on 5 August 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:

Courtesy translation – only the German version is legally binding.

Acalabrutinib

Resolution of: 5 August 2021
Entry into force on: 5 August 2021
BAnz AT DD. 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 5 August 2021):

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

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

a) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy

Appropriate comparator therapy:

- a patient-individual therapy under selection of
  - rituximab in combination with fludarabine and cyclophosphamide (FCR),
  - rituximab in combination with bendamustine (BR),
  - venetoclax in combination with rituximab and
  - rituximab in combination with chlorambucil (ClbR);

  taking into account the molecular-cytogenetic characteristics of the disease, the general condition as well as the success and tolerability of the previous therapy

Extent and probability of the additional benefit of acalabrutinib compared to the appropriate comparator therapy:

a1) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy and for whom bendamustine in combination with rituximab is the appropriate patient-individual therapy

An additional benefit is not proven.

a2) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy and for whom other than bendamustine in combination with rituximab is the appropriate patient-individual therapy

An additional benefit is not proven.

Courtesy translation – only the German version is legally binding.

b) Adult patients with chronic lymphocytic leukaemia after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons

Appropriate comparator therapy:

- Ibrutinib

or

- idelalisib in combination with rituximab

or

- best supportive care (only for patients who have failed prior therapy with ibrutinib or idelalisib in combination with rituximab)

Extent and likelihood of additional benefit of acalabrutinib over idelalisib in combination with rituximab:

Hint of a considerable additional benefit

(c) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies

Appropriate comparator therapy:

- a patient-individual therapy under selection of
  - ibrutinib,
  - idelalisib in combination with rituximab,
  - venetoclax in combination with rituximab,
  - rituximab in combination with fludarabine and cyclophosphamide (FCR),
  - rituximab in combination with bendamustine (BR),
  - rituximab in combination with chlorambucil (ClbR),
  - ibrutinib in combination with BR and
  - best supportive care;

  taking into account the molecular-cytogenetic characteristics of the disease, the general condition as well as the success and tolerability of the previous therapy

Extent and probability of the additional benefit of acalabrutinib compared to the appropriate comparator therapy:

c1) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies for whom idelalisib in combination with rituximab or rituximab in combination with bendamustine is the appropriate patient-individual therapy

Hint for a minor additional benefit

c2) *Adult patients with chronic lymphocytic leukaemia after at least two prior therapies for whom therapy other than idelalisib in combination with rituximab or rituximab in combination with bendamustine is the appropriate patient-individual therapy*

An additional benefit is not proven.

Courtesy translation – only the German version is legally binding.

Study results according to endpoints:[1]

a) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy

a1) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy and for whom bendamustine in combination with rituximab is the appropriate patient-individual therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↔	No difference relevant for the benefit assessment, in detail advantages and one disadvantage for specific adverse events.
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		

ASCEND study: Acalabrutinib vs therapy at principal investigator's discretion with choice of bendamustine + rituximab or idelalisib + rituximab

Study design: randomised, open-label, parallel

Relevant sub-population: Patients after one prior therapy for whom chemoimmunotherapy is indicated (acalabrutinib vs bendamustine + rituximab)

Data cut-offs: 15. January 2019 (interim analysis), 1 August 2019 (EMA requirement)

[1] Data from the dossier assessment of the IQWiG (A20-105) and from the addenda (A21-51, A21-87), unless otherwise indicated.

Courtesy translation – only the German version is legally binding.

Mortality[a]

Endpoint	Acalabrutinib		Bendamustine + rituximab		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio (HR) [95% CI] p-value Absolute difference (AD)[b]
Overall survival					
	17	n.a. *1 (5.9)*	19	n.a. *2 (10.5)*	0.58 [0.03; 6.01] 0.648

Morbidity

Progression-free survival (PFS) [c, d]					
Independent Review Committee (IRC)	17	n.a. *1 (5.9)*	19	19.5 [16.5; n. a.] *5 (26.3)*	0.22 [0.01; 1.36] 0.127
Fatigue (FACIT-Fatigue)[d, e]					
	17	n.a. *3 (17.6)*	19	n.a. *4 (21.1)*	0.79 [0.16; 3.59] 0.770
Disease-related symptomatology[d]					
	no usable data available[f]				
EORTC QLQ-C30 – symptom scales[d]					
Time to deterioration ≥ 15 points[g]					
Fatigue	17	n.a. *2 (11.8)*	19	n.a. *3 (15.8)*	0.78 [0.10; 4.70] 0.784
Nausea and vomiting	17	n.a. *2 (11.8)*	19	n.a. *5 (26.3)*	0.42 [0.06; 1.96] 0.294
Pain	17	13.9 [1.1; n. a.] *7 (41.2)*	19	16.8 [2.1; n. a.] *6 (31.6)*	1.53 [0.48; 5.21] 0.463
Loss of appetite	17	n.a. *1 (5.9)*	19	n.a. *5 (26.3)*	0.21 [0.01; 1.30] 0.116

Courtesy translation – only the German version is legally binding.

Diarrhoea	17	n.a. *2 (11.8)*	19	11.3 [1.0; n. a.] *7 (36.8)*	0.29 [0.04; 1.18] 0.096
Dyspnoea	17	n.a. *5 (29.4)*	19	n.a. *4 (21.1)*	1.77 [0.47; 7.16] 0.390
Insomnia	17	n.a. *5 (29.4)*	19	12.0 [1.9; n. a.] *8 (42.1)*	0.64 [0.19; 1.92] 0.433
Constipation	17	n.a. *4 (23.5)*	19	n.a. *6 (31.6)*	0.78 [0.20; 2.75] 0.704
Health status (EQ-5D VAS)[d]					
Time to deterioration ≥ 15 points[h]					
	17	n.a. *1 (5.9)*	19	n.a. *3 (15.8)*	0.36 [0.02; 2.80] 0.354

Health-related quality of life[d]

EORTC QLQ-C30 – functional scales					
Time to deterioration ≥ 15 points[h]					
Global health status	17	*n.a.* *2 (11.8)*	19	n.a. *5 (26.3)*	0.39 [0.06; 1.82] 0.252
Physical function	17	n.a. *3 (17.6)*	19	n.a. *2 (10.5)*	1.81 [0.30; 13.80] 0.508
Role function	17	n. a. *3 (17.6)*	19	n.a. *5 (26.3)*	0.62 [0.13; 2.52] 0.514
Cognitive function	17	n.a. *5 (29.4)*	19	n.a. *4 (21.1)*	1.80 [0.48; 7.28] 0.376
Emotional function	17	n.a. *4 (23.5)*	19	n.a. *4 (21.1)*	1.11 [0.26; 4.69] 0.886
Social function	17	n.a. *4 (23.5)*	19	3.7 [1.0; n. a.] *9 (47.4)*	0.47 [0.13; 1.44] 0.199

Courtesy translation – only the German version is legally binding.

Side effects[b]

Total adverse events (presented additionally)					
	16	0.2 [0.1; 0.5] *16 (100)*	18	0.2 [0.0; 0.3] *15 (83.3)*	–
Serious adverse events (SAE)					
	16	n.a. *4 (25.0)*	18	n.a. *5 (27.8)*	0.44 [0.08; 1.95] 0.289
Severe adverse events (CTCAE grade ≥ 3)					
	16	n.a. *5 (31.3)*	18	n.a. *8 (44.4)*	0.35 [0.08; 1.20] 0.103
Therapy discontinuation due to adverse events					
	16	n.a. 0 (0)	18	n.a. *1 (5.6)*	n.c. 0.346
Specific adverse events					
Cardiac disorders (SOC, AE)	16	n.d.	18	n.d.	–
Infections and infestations (SOC, severe AE[i])	16	n.a. *3 (18.8)*	18	n.a. *2 (11.1)*	0.53 [0.02; 5.54] 0.599
Bleeding [j] (severe AE[i])	16	n.a. *0 (0)*	18	n.a. *0 (0)*	n.c. n.c.
Diarrhoea (PT, AE)	16	n.a. *0 (0)*	18	n.a. *4 (22.2)*	n.c. 0.049
Headache (PT, AE)	16	n.a. *7 (43.8)*	18	n.a. *0 (0)*	n.c. 0.002
Neutropenia (PT, severe AE[i])	16	n.a. *0 (0)*	18	6.5 [3.7; 6.5] *6 (33.3)*	n.c. 0.003

[a] Data cut-off of 1 August 2019:
[b] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[c] Data from documents from the written statement procedure of the pharmaceutical company of 1 March 2021
[d] Data cut-off of 15 January 2019:
[e] The (first) clinically relevant deterioration is defined as a decrease of ≥ 7.8 points on a scale from 0 to 52 points.
[f] The analysed population contains only a maximum of 50% of randomised patients.
[g] Clinically relevant deterioration is defined as an increase of ≥ 15 points on a scale of 0 to 100 points.
[h] Clinically relevant deterioration is defined as a decrease of ≥ 15 points on a scale of 0 to 100 points.

Courtesy translation – only the German version is legally binding.

[i] operationalised as CTCAE grade ≥ 3
[j] no indication of which bleeding events constitute the AE of special interest

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; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n. c. = not calculable; n. a. = not achieved; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire Core 30; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus

a2) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy and for whom other than bendamustine in combination with rituximab is the appropriate patient-individual therapy

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

Endpoint category	**Direction of effect/ risk of bias**	**Summary**
Mortality	n. a.	There are no assessable data.
Morbidity	n. a.	There are no assessable data.
Health-related quality of life	n. a.	There are no assessable data.
Side effects	n. a.	There are no assessable data.

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

Courtesy translation – only the German version is legally binding.

b) Adult patients with chronic lymphocytic leukaemia after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↑	Benefits in the endpoints serious adverse events, severe adverse events (CTCAE grade ≥ 3), therapy discontinuations due to adverse events, and in detail predominantly benefits in specific adverse events
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		

ASCEND study: Acalabrutinib vs therapy at principal investigator's discretion with choice of bendamustine + rituximab or idelalisib + rituximab

Study design: randomised, open-label, parallel

Relevant sub-population: Patients after one prior therapy for whom chemoimmunotherapy is not indicated (acalabrutinib vs idelalisib + rituximab)

Data cut-offs: 15. January 2019 (interim analysis), 1 August 2019 (EMA requirement)

Courtesy translation – only the German version is legally binding.

Mortality[a]

Endpoint	**Acalabrutinib**		**Idelalisib + rituximab**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio (HR) [95% CI] p-value Absolute difference (AD)[b]
Overall survival					
	65	n.a. *6 (9.2)*	48	n.a. *7 (14.6)*	0.58 [0.19; 1.75] 0.322

Morbidity

Progression-free survival (PFS) [c, d]					
Independent Review Committee (IRC)	65	n.a. *9 (13.8)*	48	16.9 [13.8; n. a.] *18 (37.5)*	0.29 [0.12; 0.63] 0.001 AD: n.c.
Fatigue (FACIT-Fatigue)[d, e]					
	65	n.a. *18 (27.7)*	48	n.a. *10 (20.8)*	1.07 [0.49; 2.52] 0.865
Disease-related symptomatology[d]					
	no usable data available[f]				
EORTC QLQ-C30 – symptom scales[d]					
Time to deterioration ≥ 15 points[g]					
Fatigue	65	n.a. *17 (26.2)*	48	n.a. *9 (18.8)*	1.07 [0.49; 2.52] 0.865
Nausea and vomiting	65	n.a. *21 (32.3)*	48	15.7 [5.5; n. c.] *16 (33.3)*	0.77 [0.40; 1.50] 0.429
Pain	65	4.7 [2.8; n. c.] *33 (50.8)*	48	11.1 [3.0; n. a.] *17 (35.4)*	1.19 [0.67; 2.18] 0.569
Loss of appetite	65	16.6 [16.6; n. c.] *20 (30.8)*	48	n.a. *13 (27.1)*	0.83 [0.41; 1.71] 0.581

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Diarrhoea	65	16.6 [8.7; n. c.] *25 (38.5)*	48	n.a. *16 (33.3)*	0.84 [0.45; 1.60] 0.578
Dyspnoea	65	n.a. *18 (27.7)*	48	n.a. *12 (25.0)*	0.86 [0.42; 1.83] 0.677
Insomnia	65	n.a. *28 (43.1)*	48	n.a. *17 (35.4)*	0.95 [0.53; 1.78] 0.873
Constipation	65	n.a. *14 (21.5)*	48	n.a. *10 (20.8)*	0.80 [0.36; 1.86] 0.589
Health status (EQ-5D VAS)[d]					
Time to deterioration ≥ 15 points[h]					
	65	n.a. *12 (18.5)*	48	n.a. *11 (22.9)*	0.62 [0.27; 1.43] 0.246

Health-related quality of life[d]

EORTC QLQ-C30 – functional scales					
Time to deterioration ≥ 15 points[h]					
Global health status	65	16.7 [5.6; n. c.] *25 (38.5)*	48	n.a. *16 (33.3)*	0.94 [0.51; 1.80] 0.852
Physical functioning	65	n.a. *12 (18.5)*	48	n.a. *7 (14.6)*	0.99 [0.40; 2.66] 0.980
Role function	65	5.6 [3.0; n. c.] *35 (53.8)*	48	4.7 [2.8; n. c.] *19 (39.6)*	1.04 [0.60; 1.86] 0.887
Cognitive function	65	n.a. *24 (36.9)*	48	4.8 [3.0; n. c.] *20 (41.7)*	0.59 [0.32; 1.09] 0.084
Emotional function	65	n.a. *18 (27.7)*	48	n.a. *13 (27.1)*	0.84 [0.42; 1.76] 0.633
Social function	65	11.2 [4.7; n. c.] *29 (44.6)*	48	16.6 [2.8; n. c.] *17 (35.4)*	0.98 [0.54; 1.82] 0.952

Courtesy translation – only the German version is legally binding.

Side effects[b]

Total adverse events (presented additionally)					
	65	0.7 [0.3; 1.9] *62 (95.4)*	47	1.0 [0.5; 1.8] *47 (100.0)*	–
Serious adverse events (SAE)					
	65	n.a. *19 (29.2)*	47	10.9 [6.1; 17.3] *28 (59.6)*	0.29 [0.16; 0.53] < 0.001 AD: n.c.
Severe adverse events (CTCAE grade ≥ 3)					
	65	19.6 [8.3; n. a.] *34 (52.3)*	47	3.8 [2.3; 5.1] *44 (93.6)*	0.27 [0.16; 0.43] < 0.001 AD: + 15.8 months
Therapy discontinuations due to adverse events (≥ 1 component)					
	65	n.a. *8 (12.3)*	47	13.8 [9.2; n. a.] *27 (57.4)*	0.15 [0.06; 0.31] < 0.001 AD: n.c.
Specific adverse events					
Cardiac disorders (SOC, AE)	65	n.a. *9 (13.8)*	47	n.a. *4 (8.5)*	1.24 [0.40; 4.60] 0.723
Infections and infestations (SOC, severe AE[i])	65	n.a. *13 (20.0)*	47	n.a. *14 (29.8)*	0.44 [0.20; 0.95] 0.031 AD: n.c.
Bleeding [j] (severe AE[i])	65	n.a. *0 (0)*	47	n.a. *1 (2.1)*	n.c. 0.232
Headache (PT, AE)	65	n.a. *13 (20.0)*	47	n.a. *1 (2.1)*	10.02 [1.99; 182.05] 0.006 AD: n.c.
General disorders and administration site conditions (SOC, severe AEs[i])	65	n.a. *0 (0)*	47	n.a. *3 (6.4)*	n.c. 0.026 AD: n.c.

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Respiratory, thoracic and mediastinal disorders (SOC, severe AEs[i])	65	n.a. *0 (0)*	47	n.a. *5 (10.6)*	n.c. 0.002 AD: n.c.
Skin and subcutaneous tissue disorders (SOC, severe AE[i])	65	n.a. *2 (3.1)*	47	n.a. *6 (12.8)*	0.20 [0.03; 0.87] 0.029 AD: n.c.
Kidney failure (PT, severe AE[i])	65	n.a. *0 (0)*	47	n.a. *3 (6.4)*	n.c. 0.008 AD: n.c.
Blood and lymphatic system disorders (SOC, severe AE[i])	65	n.a. *17 (26.2)*	47	8.3 [4.2; n. c.] *23 (48.9)*	0.40 [0.21; 0.75] 0.004 AD: n.c.
Gastrointestinal disorders (SOC, severe AE[i])	65	n.a. *2 (3.1)*	47	n.a. *18 (38.3)*	0.05 [0.01; 0.16] < 0.001 AD: n.c.
Hepatobiliary disorders (SOC, severe AE[j])	65	n.a. *0 (0)*	47	n.a. *5 (10.6)*	n.c. 0.002 AD: n.c.
Metabolism and nutrition disorders (SOC, severe AE[i])	65	n.a. *2 (3.1)*	47	n.a. *6 (12.8)*	0.18 [0.03; 0.78] 0.018 AD: n.c.
Investigations (SOC, severe AE[i])	65	n.a. *3 (4.6)*	47	n.a. *9 (19.1)*	0.19 [0.04; 0.66] 0.007 AD: n.c.

[a] Data cut-off of 1 August 2019:
[b] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[c] Data from documents from the written statement procedure of the pharmaceutical company of 1 March 2021
[d] Data cut-off of 15 January 2019:
[e] The (first) clinically relevant deterioration is defined as a decrease of ≥ 7.8 points on a scale from 0 to 52 points.
[f] The analysed population contains only a maximum of 65% of randomised patients.
[g] Clinically relevant deterioration is defined as an increase of ≥ 15 points on a scale of 0 to 100 points.
[h] Clinically relevant deterioration is defined as a decrease of ≥ 15 points on a scale of 0 to 100 points.
[i] operationalised as CTCAE grade ≥ 3
[j] no indication of which bleeding events constitute the AE of special interest

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; HR = hazard ratio; CI = confidence

Courtesy translation – only the German version is legally binding.

interval; N = number of patients evaluated; n = number of patients with (at least one) event; n. c. = not calculable; n. a. = not achieved; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire Core 30; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus

(c) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies

c1) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies for whom idelalisib in combination with rituximab or rituximab in combination with bendamustine is the appropriate patient-individual therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↓	Disadvantages in the symptom scales fatigue, pain and insomnia, advantage in the symptom scale nausea/vomiting
Health-related quality of life	↓	Disadvantage in the function scale physical function
Side effects	↑	Benefits in the endpoints serious adverse events, severe adverse events (CTCAE grade ≥ 3), therapy discontinuations due to adverse events, and in detail predominantly benefits in specific adverse events

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

ASCEND study: Acalabrutinib vs therapy at principal investigator's discretion with choice of bendamustine + rituximab or idelalisib + rituximab

Study design: randomised, open-label, parallel

Relevant sub-population: Patients after at least two prior therapies (acalabrutinib vs bendamustine + rituximab or idelalisib + rituximab)

Data cut-offs: 15. January 2019 (interim analysis), 1 August 2019 (EMA requirement)

Courtesy translation – only the German version is legally binding.

Mortality[a]

Endpoint	**Acalabrutinib**		**Bendamustine + rituximab, idelalisib + rituximab**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio (HR) [95% CI] p-value Absolute difference (AD)[b]
Overall survival					
	73	n.a. *14 (19.2)*	88	n.a. *17 (19.3)*	0.97 [0.47; 1.98] 0.929

Morbidity

Progression-free survival (PFS) [c, d]					
Independent Review Committee (IRC)	73	n.a. *17 (23.3)*	88	14.0 [12.2; 17.0] *45 (51.1)*	0.32 [0.17; 0.55] < 0.001 AD: n.c.
Fatigue (FACIT-Fatigue)[d]					
	73	n.a. *20 (27.4)*	88	n.a. *18 (20.5)*	1.27 [0.66; 2.43] 0.475
Disease-related symptomatology[d]					
	no usable data available[f]				
EORTC QLQ-C30 – symptom scales[d]					
Time to deterioration ≥ 15 points[g]					
Fatigue	73	n.a. *29 (39.7)*	88	n.a. *20 (22.7)*	1.92 [1.09; 3.45] 0.026 AD: n.c.
Nausea and vomiting	73	n.a. *17 (23.3)*	88	n.a. *33 (37.5)*	0.49 [0.27; 0.87] 0.017 AD: n.c.
Pain	73	3.7 [2.0; 4.8] *43 (58.9)*	88	n.a. *32 (36.4)*	1.85 [1.17; 2.96] 0.009 AD: n.c.

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Loss of appetite	73	n.a. *19 (26.0)*	88	n.a. *28 (31.8)*	0.65 [0.35, 1.17] 0.156
Diarrhoea	73	n.a. *20 (27.4)*	88	n.a. *27 (30.7)*	0.67 [0.37; 1.21] 0.188
Dyspnoea	73	n.a. *26 (35.6)*	88	n.a. *22 (25.0)*	1.33 [0.75; 2.38] 0.332
Insomnia	73	11.2 [2.9; n.c.] *35 (47.9)*	88	n.a. *22 (25.0)*	1.99 [1.17; 3.46] 0.011 AD: n.c.
Constipation	73	n.a. *18 (24.7)*	88	n.a. *20 (22.7)*	0.99 [0.51; 1.87] 0.954
Health status (EQ-5D VAS)[d]					
Time to deterioration ≥ 15 points[h]					
	73	n.a. *24 (32.9)*	88	n.a. *26 (29.5)*	1.05 [0.60; 1.85] 0.849

Health-related quality of life

EORTC QLQ-C30 – functional scales					
Time to deterioration ≥ 15 points[h]					
Global health status	73	16.8 [5.6; n.c.] *29 (39.7)*	88	n.a. *28 (31.8)*	1.12 [0.67; 1.90] 0.665
Physical function	73	n.a. *22 (30.1)*	88	n.a. *13 (14.8)*	2.01 [1.02; 4.13] 0.045 AD: n.c.
Rrole function	73	4.8 [2.8; n.c.] *40 (54.8)*	88	9.0 [2.8; 16.9] *42 (47.7)*	1.13 [0.73; 1.75] 0.606
Cognitive function	73	6.0 [2.8; n.c.] *36 (49.3)*	88	11.0 [3.7; n. c.] *39 (44.3)*	1.06 [0.67; 1.68] 0.814
Emotional function	73	16.9 [5.7; n. c.]	88	n.a.	1.22 [0.72; 2.09]

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		29 (39.7)		*27 (30.7)*	0.451
Social function	73	16.8 [2.9; n.c.] *35 (47.9)*	88	8.4 [2.8; n. c.] *39 (44.3)*	0.97 [0.61; 1.53] 0.894

Side effects[b]

Total adverse events (presented additionally)					
	73	0.4 [0.3; 1.0] *70 (95.9)*	88	0.5 [0.2; 0.7] *83 (94.3)*	–
Serious adverse events (SAE)					
	73	n.a. *27 (37.0)*	88	10.5 [6.8; n. a.] *42 (47.7)*	0.54 [0.32; 0.88] 0.014 AD: n.c.
Severe adverse events (CTCAE grade ≥ 3)					
	73	10.2 [2.8; 19.1] *46 (63.0)*	88	1.9 [1.0; 2.8] *71 (80.7)*	0.45 [0.30; 0.67] < 0.001 AD: + 8.3 months
Therapy discontinuation due to adverse events					
	73	n.a. *14 (19.2)*	88	12.1 [8.4; 16.5] *48 (54.5)*	0.19 [0.10; 0.34] < 0.001 AD: n.c.
Specific adverse events					
Cardiac disorders (SOC, AE)	73	n.a. *11 (15.1)*	88	n.a. *8 (9.1)*	1.36 [0.54; 3.58] 0.514
Infections and infestations (SOC, severe AE[i])	73	n.a. *14 (19.2)*	88	n.a. *22 (25.0)*	0.48 [0.23; 0.98] 0.046 AD: n.c.
Bleeding [j] (severe AE[i])	73	n.a. *4 (5.5)*	88	n.a. *3 (3.4)*	1.01 [0.22; 5.20] 0.991
Headache (PT, AE)	73	n.a.	88	n.a.	3.16

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		14 (19.2)		*6 (6.8)*	[1.26; 8.98] 0.014 AD: n.c.
Blood and lymphatic system disorders (SOC, severe AE[i])	73	n.a. *24 (32.9)*	88	n.a. *42 (47.7)*	0.55 [0.32; 0.91] 0.023 AD: n.c.
Gastrointestinal disorder (SOC, severe AE[i])	73	n.a. *6 (8.2)*	88	n.a. *18 (20.5)*	0.20 [0.07; 0.49] < 0.001 AD: n.c.
Investigations (SOC, severe AE[i])	73	n.a. *5 (6.8)*	88	n.a. *18 (20.5)*	0.23 [0.08; 0.59] 0.002 AD: n.c.

[a] Data cut-off of 1 August 2019:
[b] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[c] Data from documents from the written statement procedure of the pharmaceutical company of 1 March 2021
[d] Data cut-off of 15 January 2019:
[e] The (first) clinically relevant deterioration is defined as a decrease of ≥ 7.8 points on a scale from 0 to 52 points.
[f] The analysed population contains only a maximum of 65% of randomised patients.
[g] Clinically relevant deterioration is defined as an increase of ≥ 15 points on a scale of 0 to 100 points.
[h] Clinically relevant deterioration is defined as a decrease of ≥ 15 points on a scale of 0 to 100 points.
[i] operationalised as CTCAE grade ≥ 3
[j] no indication of which bleeding events constitute the AE of special interest

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; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n. c. = not calculable; n. a. = not achieved; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire Core 30; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus

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c2) *Adult patients with chronic lymphocytic leukaemia after at least two prior therapies for whom therapy other than idelalisib in combination with rituximab or rituximab in combination with bendamustine is the appropriate patient-individual therapy*

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

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n. a.	There are no assessable data.
Morbidity	n. a.	There are no assessable data.
Health-related quality of life	n. a.	There are no assessable data.
Side effects	n. a.	There are no assessable data.
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 patient groups eligible for treatment

a) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy

approx. 660 to 2,460 patients

b) Adult patients with chronic lymphocytic leukaemia after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons.

approx. 810 to 3,020 patients

c) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies

approx. 550 to 2,060 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 Calquence (active ingredient: acalabrutinib) at the following publicly accessible link (last access: 05 February 2021):

https://www.ema.europa.eu/en/documents/product-information/calquence-epar-product-information_de.pdf

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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 chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy

Designation of the 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:	
Fludarabine + cyclophosphamide + rituximab (FCR)	
Fludarabine	€ 1,892.40
Cyclophosphamide	€ 213.69
Rituximab	€ 19,800.06
Additionally required SHI services	€ 57.55
Total:	€ 21,963.70
Bendamustine + rituximab (BR)	
Bendamustine	€ 5,078.56
Rituximab	€ 19,800.06
Additionally required SHI services	€ 57.55
Total:	€ 24,936.17
Chlorambucil + rituximab (ClbR)	
Chlorambucil	€ 165.70
Rituximab	€ 19,800.06
additionally required SHI services	€ 57.55
Total:	€ 20,023.31
Venetoclax + rituximab	
Venetoclax	€ 72,696.90
Rituximab	€ 19,800.06
Additionally required SHI services	€ 57.55
Total:	€ 92,554.51

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

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Other SHI services:

Designation 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	€ 1,458
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	18	€ 1,458
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426
Bendamustine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	12	€ 972

(b) Adult patients with chronic lymphocytic leukaemia after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons

Designation of the 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

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Designation of the therapy	Annual treatment costs/ patient
Additionally required SHI services	€ 11.40
Total:	€ 75,238.55
Idelalisib + rituximab	
Idelalisib	€ 52,040.73
Rituximab	€ 26,508.38
Additionally required SHI services	€ 61.08
Total:	€ 78,610.19
Best supportive care	
Best supportive care	Patient-individual

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

Other SHI services:

Designation of 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	8	€ 568

(c) <u>Adult patients with chronic lymphocytic leukaemia after at least two prior therapies</u>

Designation of the 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:	
Fludarabine + cyclophosphamide + rituximab (FCR)	
Fludarabine	€ 1,892.40
Cyclophosphamide	€ 213.69
Rituximab	€ 19,800.06
Additionally required SHI services	€ 57.55
Total:	€ 21,963.70
Bendamustine + rituximab (BR)	

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Designation of the therapy	Annual treatment costs/ patient
Bendamustine	€ 5,078.56
Rituximab	€ 19,800.06
Additionally required SHI services	€ 57.55
Total:	€ 24,936.17
Chlorambucil + rituximab (ClbR)	
Chlorambucil	€ 165.70
Rituximab	€ 19,800.06
additionally required SHI services	€ 57.55
Total:	€ 20,023.31
Venetoclax + rituximab	
Venetoclax	€ 72,696.90
Rituximab	€ 19,800.06
Additionally required SHI services	€ 57.55
Total:	€ 92,554.51
Ibrutinib	
Ibrutinib	€ 75,227.15
Additionally required SHI services	€ 11.40
Total:	€ 75,238.55
Ibrutinib + BR	
Ibrutinib	€ 75,227.15
Bendamustine	€ 5,078.56
Rituximab	€ 19,800.06
Additionally required SHI services	€ 68.95
Total:	€ 100,174.72
Idelalisib + rituximab	
Idelalisib	€ 52,040.73
Rituximab	€ 26,508.38
Additionally required SHI services	€ 61.08
Total:	€ 78,610.19
Best supportive care	
Best supportive care	Patient-individual

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

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Other SHI services:

Designation 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	€ 1,458
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	18	€ 1,458
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426
Bendamustine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	12	€ 972

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 5 August 2021.

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

Berlin, 5 August 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

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