Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Acalabrutinib (new therapeutic indication: mantle cell lymphoma, not eligible for autologous stem cell transplant, first-line, combination with bendamustine and rituximab)

of 18 December 2025

At their session on 18 December 2025, 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. **In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Acalabrutinib in accordance with the resolution of 18 December 2025 (chronic lymphocytic leukaemia, first-line, combination with venetoclax and obinutuzumab):**

Acalabrutinib

Resolution of: 18 December 2025
Entry into force on: 18 December 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 2 May 2025):

Calquence in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT).

Therapeutic indication of the resolution (resolution of 18 December 2025):

See new therapeutic indication according to marketing authorisation.

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

a) <u>Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant</u>

Appropriate comparator therapy:

– Individualised therapy with selection of

- Rituximab in combination with CHOP (cyclophosphamide in combination with doxorubicin, vincristine, predniso(lo)ne) [see Annex VI, XXVI. Rituximab for mantle cell lymphoma],
- VR-CAP (bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, prednisone) and
- BR (bendamustine in combination with rituximab)

if complete or partial remission is achieved after induction therapy with R-CHOP or BR followed by

- maintenance treatment with rituximab

Extent and probability of the additional benefit of acalabrutinib in combination with bendamustine and rituximab compared with the appropriate comparator therapy:

a1) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is an appropriate individualised therapy

An additional benefit is not proven.

a2) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is not an appropriate individualised therapy

An additional benefit is not proven.

Study results according to endpoints:[1]

a1) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is an appropriate individualised 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 for pain and diarrhoea.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↓	Disadvantage in the endpoint of therapy discontinuation due to 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 ∅: No data available. n.a.: not assessable		

[1] Data from the dossier assessment of the IQWiG (A25-89) and from the addendum (A25-143), unless otherwise indicated.

ECHO study: double-blind, randomised, controlled phase III study

- Acalabrutinib in combination with BR versus placebo in combination with BR
- Data cut-off from 12 August 2024 for overall mortality (required by the US Food and Drug Administration (FDA))
- Data cut-off from 15 February 2024 for the other endpoints (pre-specified interim analysis after approximately 250 events in progression-free survival)

Mortality

Endpoint	**Acalabrutinib + BR**		**BR**		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 [95% CI] p value
Overall survival[a]					
	299	n.r. [72.1; n.c.] 105 (35.1)	299	n.r. [73.8; n.c.] 113 (37.8)	0.87 [0.67; 1.14][b]; n.d.

Morbidity

Endpoint	**Acalabrutinib + BR**		**BR**		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 (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[c]
Progression-free survival (PFS)[d, e]					
	299	66.4 [55.1; n.c.] 110 (36.8)	299	49.6 [36.0; 64.1] 137 (45.8)	0.73 [0.57; 0.94] 0.0161 + 16.8 months
Symptomatology (EORTC QLQ-C30)[e, f]					
Fatigue	299	3.9 [3.7; 6.5] 190 (63.5)	299	4.1 [3.7; 7.0] 161 (53.8)	1.16 [0.94; 1.44] 0.166[g]
Nausea and vomiting	299	50.8 [32.2; n.c.] 110 (36.8)	299	39.4 [25.9; n.c.] 105 (35.1)	0.95 [0.72; 1.24] 0.696[b]
Pain	299	13.9 [10.2; 17.6] 157 (52.5)	299	21.4 [17.5; 36.1] 119 (39.8)	1.37 [1.08; 1.74] 0.011[b] - 7.5 months

Endpoint	**Acalabrutinib + BR**		**BR**		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 (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[c]
Dyspnoea	299	28.8 [21.2; 39.6] 122 (40.8)	299	28.6 [21.6; 58.2] 99 (33.1)	1.10 [0.85; 1.44] 0.475[b]
Insomnia	299	28.7 [17.6; 39.4] 126 (42.1)	299	36.4 [21.2; 69.0] 103 (34.4)	1.20 [0.92; 1.56] 0.176[b]
Appetite loss	299	24.9 [10.2; 61.3] 129 (43.1)	299	35.9 [18.4; 58.3] 105 (35.1)	1.13 [0.87; 1.46] 0.355[b]
Constipation	299	35.7 [21.5; n.c.] 112 (37.5)	299	28.6 [13.8; n.c.] 108 (36.1)	0.87 [0.67; 1.14] 0.344[b]
Diarrhoea	299	28.6 [14.3; 50.5] 119 (39.8)	299	47.2 [39.6; n.c.] 85 (28.4)	1.36 [1.03; 1.80] 0.030[b] - 18.6 months
Health status (EQ-5D VAS)[e, h]					
	299	50.7 [25.0; n.c.] 111 (37.1)	299	47.2 [35.9; n.c.] 88 (29.4)	1.18 [0.89; 1.57] 0.248[b]

Health-related quality of life

Endpoint	**Acalabrutinib + BR**		**Placebo + BR**		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 (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[c]
EORTC QLQ-C30[e, i]					
Global health status	299	13.9 [7.1; 21.3] 146 (48.8)	299	21.2 [13.8; 39.6] 117 (39.1)	1.18 [0.92; 1.51] 0.197[g]
Physical functioning	299	17.5 [10.2; 25.2] 147 (49.2)	299	13.9 [6.4; 24.6] 138 (46.2)	0.90 [0.71; 1.14] 0.385[g]
Role functioning	299	13.8 [6.8; 21.3] 161 (53.8)	299	10.1 [6.5; 17.7] 147 (49.2)	0.96 [0.76; 1.20] 0.701[g]
Emotional functioning	299	58.0 [32.5; n.c.] 95 (31.8)	299	52.4 [21.3; n.c.] 96 (32.1)	0.80 [0.60; 1.06] 0.120[b]
Cognitive functioning	299	14.3 [10.4; 25.0] 146 (48.8)	299	13.9 [10.2; 17.8] 147 (49.2)	0.88 [0.70; 1.10] 0.273[b]
Social functioning	299	10.2 [6.5; 17.5] 161 (53.8)	299	10.3 [6.5; 25.1] 137 (45.8)	1.09 [0.87; 1.38] 0.461[g]
FACT-Lym[e,j]					
Total score	299	n.r. 56 (18.7)	299	69.0 [65.0; n.c.] 46 (15.4)	1.08 [0.73; 1.60] 0.713[b]
Physical well-being[g]	299	65.3 [39.7; n.c.] 100 (33.4)	299	46.9 [24.9; n.c.] 106 (35.5)	0.87 [0.66; 1.14][b]
Social/ family well-being[k]	299	28.5 [17.7; 39.6] 125 (41.8)	299	28.3 [14.0; 32.5] 112 (37.5)	0.95 [0.74; 1.23][b]
Emotional well-being[l]	299	58.3 [47.1; n.c.] 81 (27.1)	299	n.r. 67 (22.4)	1.08 [0.78; 1.50][b]
Functional well-being[k]	299	24.9 [10.3; 39.6] 133 (44.5)	299	28.6 [17.6; 47.1] 110 (36.8)	1.12 [0.87; 1.45][g];
Lymphoma-specific subscale[m]	299	n.r. 56 (18.7)	299	n.r. 52 (17.4)	0.96 [0.66; 1.40][b]

Side effects

Endpoint	Acalabrutinib + BR		Placebo + BR		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value[n] Absolute difference (AD)[c]
Total adverse events (AEs, presented additionally)[e]					
	297	296 (99.7)	297	294 (99.0)	–
Serious adverse events (SAE) [e]					
	297	205 (69.0)	297	184 (62.0)	1.11 [0.99; 1.25] 0.074
Severe adverse events (CTCAE grade 3 or 4)					
	297	264 (88.9)	297	262 (88.2)	1.01 [0.95; 1.07] 0.865
Therapy discontinuation due to adverse events [e,o]					
	297	150 (50.5)	297	105 (35.4)	1.43 [1.18; 1.73] < 0.001 + 15.1%
Specific adverse events[e]					
Cardiac disorders (SOC, severe AEs)	297	23 (7.7)	297	18 (6.1)	1.28 [0.70; 2.32] 0.533
Bleeding (SMQ[p], AEs)	297	84 (28.3)	297	51 (17.2)	1.65 [1.21; 2.24] 0.001 + 11.1%
Severe bleeding (SMQ[p], severe AEs)[q]	297	6 (2.0)	297	10 (3.4)	0.60 [0.22; 1.63] 0.327
Infections and infestations (SOC, severe AEs)	297	122 (41.1)	297	101 (34.0)	1.21 [0.98; 1.49] 0.078
Vomiting (PT, AEs)	297	76 (25.6)	297	41 (13.8)	1.85 [1.31; 2.61] < 0.001 + 11.8%
Headache (PT, AEs)	297	90 (30.3)	297	42 (14.1)	2.14 [1.54; 2.98] < 0.001 + 16.2%
Injury, poisoning and procedural	297	7 (2.4)	297	18 (6.1)	0.39 [0.16; 0.92] 0.026

Endpoint	Acalabrutinib + BR		Placebo + BR		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value[n] Absolute difference (AD)[c]
complications (SOC, SAEs)					- 3.7%
Skin and subcutaneous tissue disorders (SOC, severe AEs)	297	47 (15.8)	297	12 (4.0)	3.92 [2.12; 7.23] < 0.001 + 11.8%
Leukopenia (PT, severe AEs)	297	30 (10.1)	297	11 (3.7)	2.73 [1.39; 5.34]; 0.002 + 6.4%
Hepatotoxicity (severe AEs) [r]	297	20 (6.7)	297	6 (2.0)	3.33 [1.36; 8.18] 0.005 + 4.7%

[a] Data cut-off from 12 August 2024
[b] Cox proportional hazards model, stratified by MIPI score; profile likelihood confidence intervals; p value based on stratified 2-sided log-rank test
[c] Information on absolute difference (AD) only in case of statistically significant difference; own calculation
[d] Information from the dossier of the pharmaceutical company
[e] Data cut-off from 15 February 2024
[f] Time to first deterioration; an increase in EORTC QLQ-C30 score by ≥ 10 points compared to the start of the study is considered as clinically relevant deterioration (scale range: 0 to 100).
[g] Cox proportional hazards model, stratified by MIPI score and region; profile likelihood confidence intervals; p value based on stratified 2-sided log-rank test
[h] Time to first deterioration; a decrease in EQ-5D VAS score by ≥ 15 points compared to the start of the study is considered as clinically relevant deterioration (scale range: 0 to 100)
[i] Time to first deterioration; a decrease in EORTC QLQ-C30 score by ≥ 10 points compared to the start of the study is considered as clinically relevant deterioration (scale range: 0 to 100)
[j] Time to first deterioration; a decrease in FACT-Lym total score by ≥ 25.2 points compared to the start of the study is considered as clinically relevant deterioration (scale range: 0 to 168)
[k] A decrease by ≥ 4.2 points compared to the start of the study is considered as clinically relevant deterioration (scale range: 0 to 28).
[l] A decrease by ≥ 3.6 points compared to the start of the study is considered as clinically relevant deterioration (scale range: 0 to 24).
[m] A decrease by ≥ 9 points compared to the start of the study is considered as clinically relevant deterioration (scale range: 0 to 60).

Endpoint	Acalabrutinib + BR		Placebo + BR		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value[n] Absolute difference (AD)[c]

[n] IQWiG's own calculation, unconditional exact test (CSZ method according to Martin Andrés A. et al, 1994)
[o] Discontinuation of at least one active ingredient component
[p] Operationalised via SMQ Bleeding without events based on laboratory values
[q] During operationalisation of severe haemorrhages according to the study design (with the inclusion of SAEs and CNS haemorrhages in addition to severe AEs according to CTCAE grade ≥ 3 of SMQ Bleeding), seven events occurred in the intervention arm and 16 events in the comparator arm. This results in an RR [95% CI] of 0.44 [0.18; 1.05] and a p value of 0.060
[r] Operationalised via severe AEs of the SMQs liver failure, fibrosis and cirrhosis and other diseases caused by liver damage (narrow); hepatitis, non-infectious (narrow); liver-related investigations, clinical signs and symptoms (narrow)

Abbreviations used:
AD = absolute difference; BR = bendamustine in combination with rituximab; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma; HR = hazard ratio; n.d. = no data available; CI = confidence interval; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MIPI = MCL International Prognostic Index; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire – Core 30; RR = relative risk; SMQ = standardised MedDRA query; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus; CNS = central nervous system

a2) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is not an appropriate individualised therapy

No data are available to allow an 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 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
∅: No data available.
n.a.: not assessable

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

a1) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is an appropriate individualised therapy

Approx. 90 to 190 patients

a2) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is not an appropriate individualised therapy

Approx. 130 to 270 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: 30 September 2025):

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

Treatment with acalabrutinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with mantle cell lymphoma.

4. Treatment costs

Annual treatment costs:

The costs for the first year of treatment are shown for the cost representation in the resolution.

Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Acalabrutinib	€ 75,182.09
Bendamustine	€ 6,148.05
Rituximab	€ 16,151.40 - € 24,227.10
Total	*€ 97,481.54 - € 105,557.24*

Appropriate comparator therapy:	
Bendamustine + rituximab	
Bendamustine	€ 6,148.05
Rituximab	€ 16,151.40 - € 24,227.10
Total	*€ 22,299.45 - € 30,375.15*
R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)	
Rituximab	€ 21,714.40 - € 31,214.46
Cyclophosphamide	€ 526.48
Doxorubicin	€ 2,098.48
Vincristine	€ 280.32
Prednisone	€ 123.24
Total	*€ 24,742.92 - € 34,242.98*
VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone)	
Rituximab	€ 16,151.40 - € 21,535.20
Bortezomib	€ 4,208.16 - € 5,610.88
Cyclophosphamide	€ 394.86 - € 526.48
Doxorubicin	€ 1,573.86 - € 2,098.48
Prednisone	€ 149.70 - € 190.66
Total	*€ 22,477.98 - € 29,961.70*

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 October 2025)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Acalabrutinib + bendamustine + rituximab					
Bendamustine	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	6	12.0	€ 1,200
Rituximab	Surcharge for the preparation of a parenteral solution	€ 100	6 - 9	6.0 - 9.0	€ 600 - € 900

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	containing monoclonal antibodies				
Appropriate comparator therapy:					
Bendamustine + rituximab					
Bendamustine	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	6	12.0	€ 1,200
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	6 - 9	6.0 - 9.0	€ 600 - € 900
R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	8 - 11.5	€ 800 - € 1,150
Cyclophosphamide	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	1	8.0	€ 800
Doxorubicin	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	1	8.0	€ 800
Vincristine	Surcharge for the preparation of a parenteral	€ 100	1	8.0	€ 800

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	solution containing cytostatic agents				
VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone)					
Bortezomib	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	4	6.0 – 8.0	€ 2,400 - € 3,200
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	6.0 – 8.0	€ 600 - € 800
Cyclophosphamide	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	1	6.0 – 8.0	€ 600 - € 800
Doxorubicin	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	1	6.0 – 8.0	€ 600 - € 800

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

a) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 18 December 2025.

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

Berlin, 18 December 2025

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

Prof. Hecken