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
Zanubrutinib (new therapeutic indication: chronic lymphocytic leukemia (CLL), relapsed/refractory)

of 15 June 2023

At its session on 15 June 2023, 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 Zanubrutinib in accordance with the resolution of 15 June 2023 for the therapeutic indication: "for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL)":**

Zanubrutinib

Resolution of: 15 June 2023
Entry into force on: 15 June 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 15 November 2022):

BRUKINSA as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL).

Therapeutic indication of the resolution (resolution of 15 June 2023):

Brukinsa as monotherapy is indicated for the treatment of adult patients with relapsed/refractory chronic lymphocytic leukemia (CLL).

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

a) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have neither received a BTK inhibitor nor a BCL2 inhibitor

Appropriate comparator therapy:

- Ibrutinib

or

- Venetoclax + rituximab

or

- a chemoimmunotherapy with FCR or BR or ClbR (in each case only if there is a long relapse-free interval and no genetic risk factors)

Extent and probability of the additional benefit of zanubrutinib compared to ibrutinib:

Indication of a minor additional benefit.

b) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor

Appropriate comparator therapy:

- Venetoclax + rituximab

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

An additional benefit is not proven.

c) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor

Appropriate comparator therapy:

– Ibrutinib

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

An additional benefit is not proven.

d) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and a BCL2 inhibitor

Appropriate comparator therapy:

– Patient-individual therapy with selection of:
  - idelalisib in combination with rituximab,
  - bendamustine in combination with rituximab,
  - chlorambucil in combination with rituximab and
  - best supportive care;

  taking into account comorbidities, general condition, genetic risk factors as well as success and tolerability of prior therapy

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

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have neither received a BTK inhibitor nor a BCL2 inhibitor

Indication of a minor additional benefit.

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	↑↑	Advantages in the endpoints of serious adverse events (SAEs) and discontinuation due to AEs as well as in detail for the specific AEs
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		

ALPINE study:

- Study design: RCT, open-label, parallel
- Comparison: Zanubrutinib vs ibrutinib
- Relevant data cut-off: 3rd data cut-off (final analysis) from 08.08.2022

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-132) unless otherwise indicated.

Mortality

Endpoint	Zanubrutinib		Ibrutinib		Zanubrutinib vs ibrutinib
	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
Overall survival					
	327	n.r. *48 (14.7)*	325	n.r. *60 (18.5)*	0.76 [0.51; 1.11] 0.153
Effect modification by the "age" characteristic					
< 65 years	126	n.r. *7 (5.6)*	125	n.r. *19 (15.2)*	0.35 [0.15; 0.82] 0.012
≥ 65 years	201	n.r. *41 (20.4)*	200	n.r. *41 (20.5)*	0.96 [0.62; 1.48] 0.851
Total				Interaction:	0.039

Morbidity

Endpoint	Zanubrutinib		Ibrutinib		Zanubrutinib vs ibrutinib
	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
Progression-free survival (PFS)[a]					
	327	n.r. (34.3; n.r.] *88 (26.9)*	325	35.0 [33.2; 44.3] *120 (36.9)*	0.65 [0.49; 0.86] 0.0024

Endpoint	Zanubrutinib		Ibrutinib		Zanubrutinib vs ibrutinib
	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
Symptomatology (EORTC QLQ-C30)[b]					
Fatigue	327	28.0 [22.6; n.c.] *141 (43.1)*	325	30.4 [16.6; n.c.] *136 (41.8)*	0.91 [0.72; 1.16] 0.463
Nausea and vomiting	327	n.r. [36.0; n.c.] *78 (23.9)*	325	n.r. *75 (23.1)*	0.87 [0.64; 1.20] 0.404
Pain	327	22.1 [16.6; 28.8] *161 (49.2)*	325	14.1 [11.2; 19.6] *160 (49.2)*	0.85 [0.69; 1.06] 0.158
Appetite loss	327	n.r. *84 (25.7)*	325	n.r. *78 (24.0)*	0.90 [0.66; 1.23] 0.515
Diarrhoea	327	n.r. 73 (22.3)	325	n.r. [36.1; n.c.] *89 (27.4)*	0.68 [0.50; 0.93] 0.015
Dyspnoea	327	39.4 [n.c.; n.c.] 96 (29.4)	325	43.7 [34.8; n.c.] *91 (28.0)*	0.96 [0.72; 1.28] 0.779
Insomnia	327	n.r. [30.5; n.c.] 117 (35.8)	325	n.r. [25.3; n.c.] *111 (34.2)*	0.90 [0.70; 1.17] 0.450
Constipation	327	n.r. [36.0; n.c.] *101 (30.9)*	325	36.3 [36.1; n.c.] *81 (24.9)*	1.16 [0.87; 1.55] 0.322
Health status (EQ-5D VAS)[c]					
	327	n.r. 85 (26.0)	325	n.r. [35.9; n.c.] 91 (28.0)	0.80 [0.59; 1.07] 0.128

Health-related quality of life

Endpoint	Zanubrutinib		Ibrutinib		Zanubrutinib vs ibrutinib
	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)
Symptomatology (EORTC QLQ-C30)[b]					
General health status	327	39.4 [33.2; n.c.] 119 (36.4)	325	n.r. [24.9; n.c.] 116 (35.7)	0.89 [0.69; 1.15] 0.366
Physical functioning	327	n.r. [33.1; n.c.] 118 (36.1)	325	n.r. [31.4; n.c.] 105 (32.3)	0.96 [0.74; 1.25] 0.768
Role functioning	327	30.2 [19.9; n.c.] 148 (45.3)	325	30.5 [19.4; n.c.] 130 (40.0)	1.01 [0.80; 1.28] 0.920
Cognitive functioning	327	22.1 [14.3; 25.0] 166 (50.8)	325	24.9 [16.7; n.c.] 138 (42.5)	1.09 [0.87; 1.36] 0.470
Emotional functioning	327	n.r. [36.0; n.c.] 107 (32.7)	325	n.r. 91 (28.0)	1.02 [0.77; 1.35] 0.873
Social functioning	327	27.7 [22.1; n.c.] 142 (43.4)	325	43.7 [30.6; n.c.] 107 (32.9)	1.23 [0.96; 1.59] 0.102

Side effects[d]

Endpoint	Zanubrutinib		Ibrutinib		Zanubrutinib vs ibrutinib
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value AD[e]
Adverse events (presented additionally)					
	324	318 (98.1)	324	321 (99.1)	
Serious adverse events (SAE)					
	324	136 (42.0)	324	162 (50.0)	0.84 [0.71; 0.99] 0.043 AD = 8%
Severe adverse events (CTCAE grade ≥ 3)[f]					
	324	218 (67.3)	324	228 (70.4)	0.96 [0.86; 1.06] 0.530
Discontinuation due to AEs					
	324	50 (15.4)	324	72 (22.2)	0.69 [0.50; 0.96] 0.028 AD = 6.6%
Specific adverse events					
Infections and infestations (SOC, severe AEs[f])	324	86 (26.5)	324	91 (28.1)	0.95 [0.74; 1.22] 0.753
Cardiac disorders (SOC, severe AEs[f])	324	17 (5.2)	324	31 (9.6)	0.55 [0.31; 0.97] 0.038 AD = 4.4%
Bleeding (SMQ[g], AEs)	324	137 (42.3)	324	134 (41.4)	1.02 [0.85; 1.23] 0.875
Muscle spasms (PT, AEs)	324	10 (3.1)	324	41 (12.7)	0.24 [0.12; 0.48] < 0.001 AD = 9.6%

[a] Information from the dossier of the pharmaceutical company

Endpoint	Zanubrutinib		Ibrutinib		Zanubrutinib vs ibrutinib
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value AD[e]

[b] Time to first deterioration. A decrease in the score by ≥ 10 points (for the functional scales) or an increase by ≥ 10 points (for the symptom scales) compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).

[c] Time to first deterioration. A decrease in score by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).

[d] Information refers to the safety population, which includes all patients who received any dose of the study medications (324 vs 324 patients)

[e] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation

[f] operationalised as CTCAE grade ≥ 3

[g] without events based on laboratory values

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; 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.r. = not reached; PT = preferred term; RR = relative risk; SMQ = standardised MedDRA query; SOC = system organ class; SAE: serious adverse event; AE: adverse event; VAS = visual analogue scale; vs = versus

b) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor

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		

c) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor

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		

d) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and a BCL2 inhibitor

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

a) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have neither received a BTK inhibitor nor a BCL2 inhibitor

approx. 2,000 – 3,000 patients

b) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor

approx. 4,620 – 6,060 patients

c) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor

approx. 1,410 – 2,260 patients

d) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and a BCL2 inhibitor

approx. 770 – 1,430 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 Brukinsa (active ingredient: zanubrutinib) at the following publicly accessible link (last access: 10 February 2023):

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

Treatment with zanubrutinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with chronic lymphocytic leukemia.

4. Treatment costs

Annual treatment costs:

a) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have neither received a BTK inhibitor nor a BCL2 inhibitor

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Zanubrutinib	€ 65,843.20
Appropriate comparator therapy:	
Ibrutinib monotherapy	
Ibrutinib	€ 73,188.50
Venetoclax + rituximab	
Venetoclax	€ 69,760.32
Rituximab	€ 19,431.64
Total	€ 89,191.96
Additionally required SHI costs	€ 50.59
Chemoimmunotherapy with FCR or BR or ClbR	
Fludarabine + cyclophosphamide + rituximab (FCR)	
Fludarabine	€ 1,892.46
Cyclophosphamide	€ 219.48
Rituximab	€ 19,431.64
Total	€ 21,543.58
Additionally required SHI costs	€ 50.59
Bendamustine + rituximab (BR)	
Bendamustine	€ 6,022.64
Rituximab	€ 19,431.64
Total	€ 25,454.28

Designation of the therapy	Annual treatment costs/ patient
Additionally required SHI costs	€ 50.59
Chlorambucil + rituximab (ClbR)	
Chlorambucil	€ 166.10
Rituximab	€ 19,431.64
Total	€ 19,597.74
Additionally required SHI costs	€ 50.59

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 May 2023)

b) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Zanubrutinib	€ 65,843.20
Appropriate comparator therapy:	
Venetoclax + rituximab	
Venetoclax	€ 69,760.32
Rituximab	€ 19,431.64
Total	€ 89,191.96
Additionally required SHI costs	€ 50.59

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 May 2023)

c) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Zanubrutinib	€ 65,843.20
Appropriate comparator therapy:	
Ibrutinib monotherapy	
Ibrutinib	€ 73,188.50

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 May 2023)

d) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and a BCL2 inhibitor

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Zanubrutinib	€ 65,843.20
Appropriate comparator therapy:	
Idelalisib in combination with rituximab	
Idelalisib	€ 49,818.61
Rituximab	€ 26,005.24
Total	€ 75,823.85
Additionally required SHI costs	€ 50.59
Bendamustine in combination with rituximab	
Bendamustine	€ 6,022.64
Rituximab	€ 19,431.64
Total	€ 25,454.28
Additionally required SHI costs	€ 50.59
Chlorambucil in combination with rituximab	
Chlorambucil	€ 166.10
Rituximab	€ 19,431.64
Total	€ 19,597.74
Additionally required SHI costs	€ 50.59
Best supportive care	
Best supportive care[2]	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 May 2023)

[2] In the case of a comparison with best supportive care, also to be used additionally for the medicinal product to be assessed.

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ Cycle	Number/ patient/ year	Costs/ patient/ year
Venetoclax in combination with rituximab					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	Cycle 1: 1 Cycle 2 - 6: 1	6	€ 600
Fludarabine in combination with cyclophosphamide and rituximab [FCR]					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	Cycle 1: 1 Cycle 2 - 6: 1	6	€ 600
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	18	€ 1800
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	18	€ 1800
Bendamustine in combination with rituximab [BR]					
Bendamustine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	12	€ 1200
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	6	€ 600

Designation of the therapy	Type of service	Costs/ unit	Number/ Cycle	Number/ patient/ year	Costs/ patient/ year
Chlorambucil in combination with rituximab					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	6	€ 600
Idelalisib in combination with rituximab					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	8	€ 800

5. 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 Zanubrutinib

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with zanubrutinib for the treatment of adult patients with relapsing/refractory chronic lymphocytic leukemia (CLL) on the basis of the marketing authorisation granted under Medicinal Products Act:

a) <u>Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have neither received a BTK inhibitor nor a BCL2 inhibitor</u>

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b) <u>Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor</u>

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

c) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

d) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and a BCL2 inhibitor

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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 15 June 2023.

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

Berlin, 15 June 2023

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

Prof. Hecken