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), first-line)

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 16 June 2022:

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 previously untreated chronic lymphocytic leukemia (CLL).

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

Adults with previously untreated chronic lymphocytic leukemia (CLL)

Appropriate comparator therapy for zanubrutinib:

- Ibrutinib

or

- Ibrutinib in combination with rituximab or obinutuzumab

or

- Fludarabine in combination with cyclophosphamide and rituximab [FCR] (only for patients without genetic risk factors and < 65 years of age who are eligible for therapy with FCR on the basis of their general condition and comorbidities)

or

- Bendamustine in combination with rituximab (only for patients without genetic risk factors and who are ineligible for therapy with FCR according to the above criteria)

or

- Chlorambucil in combination with rituximab or obinutuzumab (only for patients without genetic risk factors and who are ineligible for therapy with FCR according to the above criteria)

a) Adults with previously untreated chronic lymphocytic leukemia (CLL) without genetic risk factors who are ineligible for therapy with FCR on the basis of their general condition and comorbidities

Extent and probability of the additional benefit of zanubrutinib over bendamustine in combination with rituximab

Hint for a minor additional benefit

b) Adults with previously untreated chronic lymphocytic leukemia (CLL) without genetic risk factors who are eligible for therapy with FCR on the basis of their general condition and comorbidities and adults with previously untreated chronic lymphocytic leukemia (CLL) with genetic risk factors

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 previously untreated chronic lymphocytic leukemia (CLL) without genetic risk factors who are ineligible for therapy with FCR on the basis of their general condition and comorbidities

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 severe AEs and discontinuation due to AEs as well as predominantly in detail for 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		

[1] Data from the dossier assessment of the IQWiG (A22-130) and from the addendum (A23-41), unless otherwise indicated.

SEQUOIA study
Study design: open-label, randomised, controlled, phase 3
Comparison: Zanubrutinib vs bendamustine in combination with rituximab
Data cut-off: 7 March 2022
Sub-population: Patients from cohort 1 who do not have a TP53 mutation and a mutated IGHV status

Mortality

Endpoint	**Zanubrutinib**		**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 (%)*	HR [95% CI] p value
Overall survival					
	104	n.r. *6 (5.8)*	106	n.r. *10 (9.4)*	0.54 [0.20; 1.49] 0.113

Morbidity

Endpoint	**Zanubrutinib**		**Bendamustine + rituximab**		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[b]					
	104	n.r. [n.r.; n.r.] *13 (12.5)*	106	44.0 [39.2; n.r.] *29 (27.4)*	0.37 [0.19; 0.70] 0.0009
Symptomatology - Symptom scales of the EORTC QLQ-C30[c]					
Fatigue	104	19.4 [11.2; 30.8] *58 (55.8)*	106	11.1 [5.9; 33.2] *48 (45.3)*	0.85 [0.58; 1.25] 0.415
Nausea and vomiting	104	n.r. *30 (28.8)*	106	n.r. [38.9; n.c.] *27 (25.5)*	0.83 [0.49; 1.40] 0.491
Pain	104	11.6 [5.9; 19.7] *64 (61.5)*	106	12.2 [8.4; 22.2] *49 (46.2)*	1.12 [0.77; 1.63] 0.541

Endpoint	**Zanubrutinib**		**Bendamustine + rituximab**		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Appetite loss	104	n.r. [36.3; n.c.] *33 (31.7)*	106	n.r. [30.7; n.c.] *31 (29.2)*	0.75 [0.46; 1.23] 0.253
Diarrhoea	104	39.3 [33.4; n.c.] *37 (35.6)*	106	n.r. [21.7; n.c.] *32 (30.2)*	0.90 [0.56; 1.44] 0.655
Dyspnoea	104	n.r. [25.1; n.c.] *42 (40.4)*	106	n.r. [33.3; n.c.] *30 (28.3)*	1.13 [0.71; 1.80] 0.617
Insomnia	104	30.5 [16.9; n.c.] *49 (47.1)*	106	39.3 [21.8; n.c.] *35 (33.0)*	1.06 [0.69; 1.64] 0.790
Constipation	104	n.r. [36.0; n.c.] *35 (33.7)*	106	n.r. [27.7; n.c.] *29 (27.4)*	0.95 [0.58; 1.55] 0.827
Health status					
(EQ-5D VAS)[d]	104	n.r. [38.9; n.c.] *34 (32.7)*	106	n.r. *22 (20.8)*	1.24 [0.72; 2.12] 0.431

Health-related quality of life

Endpoint	**Zanubrutinib**		**Bendamustine + rituximab**		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Functional scales of the EORTC QLQ-C30[c]					
General health status	104	30.8 [14.1; n.c.] *50 (48.1)*	106	33.1 [8.4; n.c.] *42 (39.6)*	0.91 [0.60; 1.37] 0.640
Physical functioning	104	38.9 [33.3; n.c.] *38 (36.5)*	106	n.r. [19.6; n.c.] *32 (30.2)*	0.84 [0.52; 1.34] 0.461
Role functioning	104	33.7 [22.2; n.c.] *46 (44.2)*	106	16.4 [8.3; 28.3] *48 (45.3)*	0.61 [0.41; 0.92] 0.016 AD: + 17.3 months
Cognitive functioning	104	16.6 [10.3; 20.1] *63 (60.6)*	106	14.2 [11.6; 24.9] *46 (43.4)*	1.15 [0.79; 1.68] 0.478
Emotional functioning	104	n.r. [33.2; n.c.] *38 (36.5)*	106	n.r. [22.2; n.c.] *33 (31.1)*	0.91 [0.57; 1.45] 0.693
Social functioning	104	30.8 [17.3; n.c.] *49 (47.1)*	106	14.2 [6.6; 30.6] *48 (45.3)*	0.69 [0.46; 1.03] 0.070

Side effects

Endpoint	Zanubrutinib		Bendamustine + rituximab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[a]
Adverse events in total					
	104	*101 (97.1)*	101	*98 (97.0)*	
Serious adverse events (SAE)					
	104	*50 (48.1)*	101	*49 (48.5)*	0.99 [0.75; 1.32] > 0.999
Severe adverse events (CTCAE grade ≥ 3)					
	104	*59 (56.7)*	101	*82 (81.2)*	0.70 [0.58; 0.85] < 0.001 AD: 15.6%
Therapy discontinuations due to adverse events[e]					
	104	n.r. [44.1; n.c.] *10 (9.6)*	101	n.r. *14 (13.9)*	HR: 0.06 [0.01; 0.48] < 0.001 AD: 4.3%
Specific adverse events					
Haemorrhage (SMQ[f], AEs)	104	*53 (51.0)*	101	12 (11.9)	4.29 [2.44; 7.54] < 0.001 AD: 39.1%
Haemorrhage (SMQ[f], severe AEs (CTCAE grade ≥ 3))	104	*4 (3.8)*	101	1 (1.0)	3.88 [0.44; 34.16] 0.245
Cardiac disorders (SOC, severe AEs (CTCAE grade ≥ 3))	104	*8 (7.7)*	101	4 (4.0)	1.94 [0.60; 6.25] 0.269
Infections and infestations (SOC, severe AEs (CTCAE grade ≥ 3))	104	*22 (21.2)*	101	20 (19.8)	1.07 [0.62; 1.83] 0.848
Response in relation to an infusion	Evaluations unsuitable				

Endpoint	Zanubrutinib		Bendamustine + rituximab		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[a]
Nausea (PT, AEs)	104	*13 (12.5)*	101	*34 (33.7)*	0.37 [0.21; 0.66] < 0.001
Contusion (PT, AEs)	104	*27 (26.0)*		*4 (4.0)*	6.56 [2.38; 18.07] < 0.001
Hypotension (PT, AEs)	104	*3 (2.9)*		*14 (13.9)*	0.21 [0.06; 0.70] 0.005
Fever (PT, AEs)	104	1 (1.0)	101	*9 (8.9)*	0.11 [0.01; 0.84] 0.008
Blood and lymphatic system disorders (SOC, severe AEs (CTCAE grade ≥ 3))	104	*17 (16.3)*	101	*42 (41.6)*	0.39 [0.24; 0.64] < 0.001
Investigations (SOC, severe AEs (CTCAE grade ≥ 3))	104	*6 (5.8)*	101	*17 (16.8)*	0.34 [0.14; 0.83] 0.012

[a] Indication of absolute difference (AD) only in case of statistically significant difference, insofar as calculable; own calculation.
[b] Data from Module 4 of the dossier.
[c] Time to first deterioration. An increase (symptomatology) or decrease (health-related quality of life) of the EORTC QLQ-C30 score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[d] Time to first deterioration. A decrease of the EQ-5D VAS score by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[e] The fixed treatment duration and the associated discontinuation of observation in the comparator arm means that the hazard ratio only reflects approximately the first 8 months post randomisation.
[f] Without events based on laboratory values

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; 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; SOC = system organ class; SMQ = standardised MedDRA query; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

b) Adults with previously untreated chronic lymphocytic leukemia (CLL) without genetic risk factors who are eligible for therapy with FCR on the basis of their general condition and comorbidities and adults with previously untreated chronic lymphocytic leukemia (CLL) with genetic risk factors

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

Adults with previously untreated chronic lymphocytic leukemia (CLL)

approx. 3,190 – 3,200 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:

Adults with previously untreated chronic lymphocytic leukemia (CLL)

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
Ibrutinib in combination with rituximab	
Ibrutinib	€ 73,188.50
Rituximab	€ 19,431.64
Total:	€ 92,620.14
Additionally required SHI services	€ 50.59
Ibrutinib in combination with obinutuzumab	
Ibrutinib	€ 73,188.50
Obinutuzumab	€ 19,147.84
Total:	€ 92,336.34
Additionally required SHI services	€ 138.70
Fludarabine in combination with cyclophosphamide and rituximab [FCR]	
Fludarabine	€ 1,892.46
Cyclophosphamide	€ 219.48
Rituximab	€ 19,431.64
Total:	€ 21,543.58
Additionally required SHI services	€ 50.59
Bendamustine in combination with rituximab	
Bendamustine	€ 6,022.64
Rituximab	€ 19,431.64
Total:	€ 25,454.28
Additionally required SHI services	€ 50.59
Chlorambucil in combination with rituximab	
Chlorambucil	€ 166.10
Rituximab	€ 19,431.64
Total:	€ 19,597.74
Additionally required SHI services	€ 50.59

Designation of the therapy	Annual treatment costs/ patient
Chlorambucil in combination with obinutuzumab	
Chlorambucil	€ 166.10
Obinutuzumab	€ 19,147.84
Total:	€ 19,313.94
Additionally required SHI services	€ 138.70

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

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Ibrutinib in combination with rituximab					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	Cycle 1: 2 Cycle 2 - 6: 1	7	€ 700
Ibrutinib in combination with obinutuzumab					
Obinutuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	Cycle 1: 4 Cycle 2 - 6: 1	8 - 9	€ 800 - € 900
Fludarabine in combination with cyclophosphamide and rituximab [FCR]					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	6	€ 600
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	18	€ 1800

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
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
Chlorambucil in combination with rituximab					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	6	€ 600
Chlorambucil in combination with obinutuzumab					
Obinutuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	Cycle 1: 4 Cycle 2 - 6: 1	8 - 9	€ 800 - € 900

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 previously untreated chronic lymphocytic leukemia (CLL) on the basis of the marketing authorisation granted under Medicinal Products Act:

Adults with previously untreated chronic lymphocytic leukemia (CLL)

- 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