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)
Ibrutinib (New Therapeutic Indication: Chronic Lymphocytic Leukaemia, First-line, Combination with Venetoclax)

of 20 July 2023

At its session on 20 July 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. 4 to the information on the benefit assessment of Ibrutinib in accordance with the resolution of 1 April 2021:

Ibrutinib

Resolution of: 20 July 2023
Entry into force on: 20 July 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 02 August 2022):

Imbruvica as a single agent or in combination with rituximab or obinutuzumab or venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Therapeutic indication of the resolution (resolution of 20 July 2023):

Imbruvica in combination with venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

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

<u>Adults with previously untreated chronic lymphocytic leukaemia (CLL)</u>

Appropriate comparator therapy:

- 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)

Extent and probability of the additional benefit of ibrutinib in combination with venetoclax compared to chlorambucil in combination with obinutuzumab

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

An additional benefit is not proven.

Extent and probability of the additional benefit of ibrutinib in combination with venetoclax compared to the appropriate comparator therapy

b) Adults with previously untreated chronic lymphocytic leukaemia (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 leukaemia (CLL) with genetic risk factors

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults with previously untreated chronic lymphocytic leukaemia (CLL) without the presence of 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	↔	Overall, no differences relevant for the benefit assessment; disadvantage in the endpoint of diarrhoea.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment.
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		

[1] Data from the dossier assessment of the IQWiG (A23-04) and from the addendum (A23-54), unless otherwise indicated.

Endpoint category	Direction of effect/ risk of bias	Summary
↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

GLOW study: Ibrutinib + venetoclax vs chlorambucil + obinutuzumab

Study design: randomised, open-label

Relevant sub-population: Patients without genetic risk factors for whom therapy with FCR is unsuitable

Data cut-offs used:

- 1st data cut-off: 26 February 2021 (morbidity (except progression-free survival, health-related quality of life)
- 3rd data cut-off: 17 January 2022 (mortality, morbidity (progression-free survival), side effects)

Mortality

Endpoint	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs chlorambucil + obinutuzumab
	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[a] Absolute difference (AD)[b]
Overall survival (3rd data cut-off: 17 January 2022)					
	23	n.a. *1 (4.3)*	24	n.a. [38.73; n.c.] *3 (12.5)*	0.34 [0.04; 3.30] p = 0.353

Morbidity

Endpoint	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs chlorambucil + obinutuzumab
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
Progression-free survival (PFS) (3rd data cut-off: 17.01.2022)[c]					
IRC	23	n.r. [n.r.; n.r.] *2 (8.7%)*	24	31.34 [23.95; n.r.] *12 (50%)*	0.14[d] [0.03; 0.62] p = 0.0097
INV	23	n.a. [n.r.; n.r.] *2 (8.7%)*	24	n.a. [31.08; n.r.] *9 (37.5%)*	0.20[d] [0.04; 0.94] p = 0.0416
Symptomatology (EORTC QLQ-C30) (1st data cut-off: 26.02.2021)[e]					
Fatigue	23	5.82 [1.87; 8.67] *13 (56.5)*	24	6.26 [2.37; n.c.] *11 (45.8)*	1.75 [0.78; 3.92] p = 0.174
Nausea and vomiting	23	13.83 [5.62; n.c.] *9 (39.1)*	24	n.a. [13.86; n.c.] *6 (25.0)*	2.17 [0.77; 6.12] p = 0.144
Pain	23	11.30 [3.91; n.c.] *11 (47.8)*	24	16.62 [3.94; 27.86] *13 (54.2)*	1.11 [0.50; 2.49] p = 0.790
Dyspnoea	23	n.a. [5.82; n.c.] *8 (34.8)*	24	13.93 [3.71; n.c.] *11 (45.8)*	0.79 [0.32; 1.97] p = 0.619
Insomnia	23	14.09 [3.75; n.c.] *9 (39.1)*	24	31.38 [2.37; n.c.] *10 (41.7)*	1.01 [0.41; 2.48] p = 0.988
Appetite loss	23	10.97 [2.56; n.c.] *10 (43.5)*	24	n.a. [6.77; n.c.] *5 (20.8)*	2.87 [0.98; 8.40] p = 0.055
Constipation	23	n.a. [5.58; n.c.] *7 (30.4)*	24	n.a. [8.35; n.c.] *5 (20.8)*	1.83 [0.58; 5.78] p = 0.301
Diarrhoea	23	8.51 [3.78; n.c.]	24	n.a. [13.86; n.c.]	3.11 [1.07; 9.00]

Endpoint	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs chlorambucil + obinutuzumab
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
		11 (47.8)		*5 (20.8)*	p = 0.037
Symptomatology (FACIT fatigue) (1st data cut-off: 26.02.2021)[f]					
Fatigue	23	n.a. [8.48; n.c.] *6 (26.1)*	24	n.a. [20.40; n.c.] *6 (25.0)*	1.24 [0.40; 3.86] p = 0.707
Health status (EQ-5D VAS) (1st data cut-off: 26.02.2021)[g]					
	23	n.a. [5.82; n.c.] *7 (30.4)*	24	n.a. [24.18; n.c.] *4 (16.7)*	2.56 [0.74; 8.76] p = 0.136

Health-related quality of life

Endpoint	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs chlorambucil + obinutuzumab
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
EORTC QLQ-C30 (1st data cut-off: 26.02.2021)[h]					
Global health status	23	20.50 [8.15; n.c.] *9 (39.1)*	24	24.18 [5.58; n.c.] *9 (37.5)*	1.18 [0.47; 2.96] p = 0.732
Physical functioning	23	n.a. [3.75; n.c.] *7 (30.4)*	24	n.a. [9.72; n.c.] *6 (25.0)*	1.52 [0.51; 4.53] p = 0.452
Role functioning	23	14.16 [3.75; n.c.] *11 (47.8)*	24	7.24 [2.53; n.c.] *12 (50.0)*	0.96 [0.42; 2.18] p = 0.923
Emotional functioning	23	n.a. [11.27; n.c.] *6 (26.1)*	24	18.97 [3.94; n.c.] *12 (50.0)*	0.44 [0.16; 1.18]

Endpoint	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs chlorambucil + obinutuzumab
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
					p = 0.103
Cognitive functioning	23	n.a. [3.75; n.c.] *7 (30.4)*	24	11.07 [3.71; n.c.] *11 (45.8)*	0.68 [0.26; 1.78] p = 0.435
Social functioning	23	10.97 [1.94; n.c.] *11 (47.8)*	24	20.07 [3.78; n.c.] *12 (50.0)*	1.21 [0.53; 2.75] p = 0.650

Side effects

Endpoint	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs chlorambucil + obinutuzumab
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
Total adverse events (presented additionally)					
	23	0.49 [0.26; 0.99] *23 (100)*	24	0.03 [0.03; 0.07] *24 (100)*	-
Serious adverse events (SAE)					
	23	n.a. [2.79; n.c.] *10 (43.5)*	24	n.a. [1.15; n.c.] *7 (29.2)*	1.40 [0.53; 3.69] p = 0.500
Severe adverse events (CTCAE grade ≥ 3)					
	23	3.94 [1.91; 6.01] *17 (73.9)*	24	1.53 [0.23; 3.38] *19 (79.2)*	0.67 [0.35; 1.32]; p = 0.247
Therapy discontinuation due to adverse events					
	23	n.a.	24	n.a.	0.55

Endpoint	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs chlorambucil + obinutuzumab
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
		4 (17.4)		*2 (8.3)*	[0.05; 6.07] p = 0.626
Specific adverse events					
Bleeding (bleeding (SMQ[i], AE)[k]	23	n.a. *9 (39.1)*	24	n.a. *3 (12.5)*	3.42 [0.91; 12.88] p = 0.070
Bleeding (SMQ[i], severe AE[j])	23	n.a. *2 (8.7)*	24	n.a. *0 (0)*	n.c.[l]
Cardiac disorders (SOC, severe AE[j])	23	n.a. *2 (8.7)*	24	n.a. *2 (8.3)*	0.57 [0.05; 6.24] p = 0.642
Infections and infestations (SOC, severe AE[j])	23	n.r. *3 (13.0)*	24	16.89 [6.21; n.c.] *5 (20.8)*	0.72 [0.16; 3.27] p = 0.673
Reaction in connection with an infusion	Evaluation unsuitable[m]				

Endpoint	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs chlorambucil + obinutuzumab
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]

[a] Effect, CI and p value: Cox proportional hazards model (unstratified).
[b] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation.
[c] Data from the pharmaceutical company's written statement of 23 May 2023.
[d] Hazard ratio (including 95% CI and p value) calculated using unstratified Cox proportional hazards model with treatment as the only explanatory variable.
[e] Time to first deterioration. An increase by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[f] Time to first deterioration. A decrease by ≥ 7.8 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 52)
[g] Time to first deterioration. A decrease by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100)
[h] Time to first deterioration. A decrease by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100)
[i] Without events based on laboratory values.
[j] Operationalised as CTCAE grade ≥ 3.
[k] Results for the 3rd data cut-off were not submitted as part of the statements. However, since no patients were already at risk at this point, the results from Module 4 A for the 4th data cut-off are presented here.
[l] The pharmaceutical company does not provide an effect estimate and p value as no events occurred in the comparator arm.
[m] The evaluation submitted by the pharmaceutical company is unsuitable for benefit assessment, but serious and severe infusion reactions are considered in the overall rates of SAEs and severe AEs.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue; HR = hazard ratio; INV = investigator; IRC = independent review committee; 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; SMQ = Standardised MedDRA Query; SOC = system organ class; SAE: serious adverse event; AE: adverse event; VAS = visual analogue scale; vs = versus

b) <u>Adults with previously untreated chronic lymphocytic leukaemia (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 leukaemia (CLL) with genetic risk factors</u>

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 leukaemia (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 IMBRUVICA (active ingredient: ibrutinib) at the following publicly accessible link (last access: 6 July 2023):

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

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

4. Treatment costs

Annual treatment costs:

<u>Adults with previously untreated chronic lymphocytic leukaemia (CLL)</u>

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
1st year	
Ibrutinib	€ 73,188.50
Venetoclax	€ 52,748.51
Total:	€ 125,937.01
2nd year	
Ibrutinib	€ 11,028.40
Venetoclax	€ 11,166.71
Total:	€ 22,195.11
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	€ 51.43
Ibrutinib in combination with obinutuzumab	
Ibrutinib	€ 73,188.50
Obinutuzumab	€ 19,147.84
Total:	€ 92,336.34
Additionally required SHI services	€ 139.82
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	€ 51.43
Bendamustine in combination with rituximab	
Bendamustine	€ 6,022.64

Designation of the therapy	Annual treatment costs/ patient
Rituximab	€ 19,431.64
Total:	€ 25,454.28
Additionally required SHI services	€ 51.43
Chlorambucil in combination with rituximab	
Chlorambucil	€ 166.10
Rituximab	€ 19,431.64
Total:	€ 19,597.74
Additionally required SHI services	€ 51.43
Chlorambucil in combination with obinutuzumab	
Chlorambucil	€ 166.10
Obinutuzumab	€ 19,147.84
Total:	€ 19,313.94
Additionally required SHI services	€ 139.82

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 July 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	€ 100	Cycle 1: 2	6	€ 600

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	parenteral solution containing monoclonal antibodies		Cycle 2 - 6: 1		
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
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					

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Obinutuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 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 Ibrutinib

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 ibrutinib for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) on the basis of the marketing authorisation granted under Medicinal Products Act:

Adults with previously untreated chronic lymphocytic leukaemia (CLL)

A designation of the concomitant active ingredients shall be made in a further resolution. The adoption of the resolution will be preceded by a written and oral written statement procedure pursuant to Chapter 5, Section 19 of the Regulation, in the course of which the pharmaceutical companies concerned will be given the opportunity to comment on the planned designation.

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 20 July 2023.

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

Berlin, 20 July 2023

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

Prof. Hecken