

**Ibrutinib** (New Therapeutic Indication: Chronic Lymphoblastic Leukaemia, First-line, in Combination with Rituximab)

Resolution of: 1 April 2021 / 18 January 2024  
Entry into force on: 1 April 2021 / 18 January 2024  
BAnz AT 07 05 2024 B3/ BAnz AT 15 02 2024 B6

Valid until: unlimited

**New therapeutic indication (according to the marketing authorisation of 28 August 2020:**

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

**Therapeutic indication of the resolution (resolution from 1 April 2021):**

IMBRUVICA in combination with rituximab 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**

- a) Adult patients with previously untreated chronic lymphocytic leukaemia, eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

**Appropriate comparator therapy:**

- Fludarabine in combination with cyclophosphamide and rituximab (FCR)

**Extent and probability of the additional benefit of ibrutinib in combination with rituximab compared to fludarabine in combination with cyclophosphamide and rituximab (FCR):**

Hint for a considerable additional benefit

- b) Adult patients with previously untreated chronic lymphocytic leukaemia, not eligible for therapy with FCR

**Appropriate comparator therapy:**

- Bendamustine in combination with rituximab

or

- Chlorambucil in combination with rituximab or obinutuzumab

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

An additional benefit is not proven.

- c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons

**Appropriate comparator therapy:**

- Ibrutinib

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

An additional benefit is not proven.

**Study results according to endpoints:<sup>1</sup>**

- a) Adult patients with previously untreated chronic lymphocytic leukaemia, eligible for a therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

**Summary of results for relevant clinical endpoints**

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	↔	no statistically significant difference
Health-related quality of life	∅	No data available.
Side effects	↑	Mainly advantages with severe AE, discontinuation because of AE and specific AE
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		

ECOG-E1912 study: Ibrutinib + rituximab vs fludarabine + cyclophosphamide + rituximab

Relevant sub-population: Patients eligible for a FCR therapy

<sup>1</sup> Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A20-88) unless otherwise indicated.

## Mortality

Endpoint	Ibrutinib + rituximab		FCR		Ibrutinib + rituximab vs FCR
	N	Median time to event in months [95 %-CI] <i>Patients with event n (%)</i>	N	Median time to event in months [95 %-CI] <i>Patients with event n (%)</i>	[95 %- CI] p value Absolute difference (AD) <sup>a</sup>
<b>Overall survival</b>					
Main analysis 1. Data cut-off (17.07.2018)	141	n.a. 0 (0)	65	n.a. 6 (9.2)	n.a. < 0.001 AD: n.c.
Main analysis 2. Data cut-off (02.08.2019)	141	n.a. 0 (0)	65	n.a. 7 (10.8)	n.a. < 0.001 AD: n.c.
Sensitivity analysis 2. Data cut-off <sup>b</sup>	141	n.a. 1 (0.7)	65	n.a. 7 (10.8)	0.06 [0.01; 0.48] < 0.001 AD: n.c.

## Morbidity

<b>Progression-free survival (PFS) <sup>c</sup></b>							
	141	n.a. [n.a.; n.a.] 17 (12.1)		65	57.3. [43,99; n.a.] 23 (35.4)		0.25 [0.14; 0.48] < 0.0001 AD: n.c.
	N	Values at the start of the study MV (SD)	Mean change in the course of study MV (SE)	N	Values at the start of the study MV (SD)	Mean change in the course of study MV (SE)	MD [95 %- CI] p value
<b>FACT-Leu TOI</b>							
FACT-Leu TOI <sup>d</sup>	139	93.2 (19.0)	6.0 (1.0)	64	93.5 (17.4)	8.1 (1.5)	-2.04 [-5.58; 1.50] 0.258
PWB	140	22.8 (5.4)	0.4 (0.3)	65	23.5 (4.2)	0.5 (0.4)	-0.08 [-1.11; 0.95]
FWB	140	20.6 (5.7)	1.1 (0.3)	65	20.3 (5.5)	1.8 (0.4)	-0.74 [-1.77; 0.30]
Leu	139	49.6 (9.9)	4.5 (0.5)	64	49.8 (9.5)	5.9 (0.8)	-1.41 [-3.27; 0.46]

## Health-related quality of life

Not collected

## Side effects

Endpoint	Ibrutinib + rituximab		FCR		Ibrutinib + rituximab vs FCR
	N	Median time to event in months [95 %-CI] <i>Patients with event n (%)</i>	N	Median time to event in months [95 %-CI] <i>Patients with event n (%)</i>	HR [95 %-CI] p value Absolute difference (AD) <sup>a</sup>
<b>Total adverse events (AE) (presented additionally)</b>					
	141	1.0 [n. c; n. c.] <i>141 (100.0)</i>	65	1.0 [n. c; n. c.] <i>65 (100.0)</i>	–
<b>Serious adverse events (SAE)</b>					
No results available					
<b>Severe adverse events (CTCAE grade ≥ 3)</b>					
	141	1.9 [1.0; 1.9] <i>126 (89.4)</i>	65	1.0 [1.0; 1.9] <i>59 (90.8)</i>	0.71 [0.52; 0.97] 0.035 AD: +0.9 months
<b>Discontinuation because of AE (≥ 1 component)</b>					
	141	n.a. <i>15 (10.6)</i>	65	n.a. <i>8 (12.3)</i>	0.29 [0.10; 0.86] 0.025 AD: n.c.
<b>Specific adverse events</b>					
Haemorrhages					
severe haemorrhages (SMQ haemorrhage terms [excl. laboratory terms] <sup>f</sup> . severe AE <sup>e</sup> ) <sup>g</sup>	141	n.a. <i>1 (0.7 %)</i>	65	n.a. <i>0 (0)</i>	n.c.
haemorrhages (SMQ haemorrhage terms [excl. laboratory terms] <sup>f</sup> . AE) <sup>g</sup>	141	37.7 <i>66 (46.8)</i>	65	n.a. <i>6 (9.2)</i>	3.46 [1.47; 8.12] 0.0044 AD: n.c.

Contusion (PT. AE)	141	n.a. 41 (29.1)	65	n.a. 3 (4.6)	4.47 [1.36; 14.70] 0.014 AD: n.c.
Infections and infestations (SOC. AE)	141	21.2 [12.9; 26.7] 90 (63.8)	65	n. a. [5.6; n. c.] 24 (36.9)	0.78 [0.48; 1.28] 0.323
Upper respiratory tract infection (PT. AE)	141	n. a. [40.5; n. c.] 50 (35.5)	65	n.a. 17 (26.2)	0.31 [0.15; 0.63] 0.001 AD: n.c.
Heart diseases (SOC. severe AE <sup>e</sup> )	141	n.a. 11 (7.8)	65	n.a. 0 (0)	n.a. 0.266
Nausea (PT. AE)	141	37.8 [12.9; n. a.] 69 (48.9)	65	1.0 [1.0; 2.8] 45 (69.2)	0.42 [0.28; 0.62] < 0.001 AD: + 36.8 months
Constipation (PT. AE)	141	n.a. 29 (20.6)	65	n.a. 22 (33.8)	0.33 [0.18; 0.61] < 0.001 AD: n.c.
Vomiting (PT. AE)	141	n.a. 28 (19.9)	65	n.a. 20 (30.8)	0.30 [0.15; 0.58] < 0.001 AD: n.c.
Decreased appetite (PT. AE)	141	n.a. 21 (14.9)	65	n.a. 17 (26.2)	0.37 [0.18; 0.74] 0.005 AD: n.c.
Pollakiuria (PT. AE)	141	n.a. 8 (5.7)	65	n.a. 8 (12.3)	0.18 [0.05; 0.63] 0.007 AD: n.c.
Lymphopenia (PT. severe AE <sup>e</sup> )	141	n.a. 12 (8.5)	65	2.8 [1.9; 3.7] 49 (75.4)	0.03 [0.01; 0.08] < 0.001 AD: n.c.
Leukopenia (PT. severe AE <sup>e</sup> )	141	n.a. 11 (7.8)	65	n. a. [5.6; n. c.] 25 (38.5)	0.06 [0.02; 0.17] < 0.001 AD: n.c.
febrile neutropenia (PT. severe AE <sup>e</sup> )	141	n.a. 1 (0.7)	65	n.a. 8 (12.3)	0.05 [0.01; 0.41] 0.005 AD: n.c.
Thrombocytopenia (PT. severe AE <sup>e</sup> )	141	n.a. 2 (1.4)	65	n.a. 4 (6.2)	0.11 [0.01; 0.97] 0.047 AD: n.c.
Leukocytosis (PT. severe AE <sup>e</sup> )	141	n.a.	65	n.a.	8.02 [1.07; 60.28]

		21 (14.9)		1 (1.5)	0.043 AD: n.c.
Lymphocytosis (PT. severe AEs <sup>e</sup> )	141	1.9 [1.9; n. a.] 78 (55.3)	65	n.a. 17 (26.2)	2.16 [1.28; 3.66] 0.004 AD: n.c.
Hyperglycemia (PT. severe AEs <sup>d</sup> )	141	n.a. 6 (4.3)	65	n.a. 4 (6.2)	0.15 [0.02; 0.96] 0.045 AD: n.c.

<sup>A</sup> Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

<sup>b</sup> Information from the dossier of the pharmaceutical company; 2nd data cut-off

<sup>c</sup> For calculating the effect estimates and confidence intervals one event was imputed in the intervention arm.

<sup>d</sup> Higher (increasing) values mean better well-being; positive effects (intervention minus control) mean an advantage for the intervention.

<sup>e</sup> operationalised as CTCAE grade  $\geq 3$

<sup>f</sup> "Excluding laboratory terms" means that the SMQ does not contain PTs resulting from laboratory tests.

<sup>g</sup> Data subsequently submitted from the pU of the written statement procedure

Abbreviations used:

AD = Absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; FACT-Leu: Functional Assessment of Cancer Therapy – Leukaemia; FCR = FCR: Fludarabin + cyclophosphamide + rituximab; FWB: Functional well-being; HR = Hazard ratio; n.d. = no data available; CI = confidential interval; MedDRA = Medical Dictionary for Regulatory Activities; FWB: Functional well-being; MD: mean difference; MV: Mean value; N = number of patients evaluated; n= number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PWB: Physical well-being; PT = Preferred term; SD: Standard deviation; SE: Standard error; SMQ: Standardised MedDRA Query; SOC: system organ class; vs. versus; TOI: Trial Outcome Index

- b) Adult patients with previously untreated chronic lymphocytic leukaemia. not eligible for a therapy with FCR

### 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

∅: There are no usable data for the benefit assessment.

n.a.: not assessable

- c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons

### Summary of results for relevant clinical endpoints

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## 2. Number of patients or demarcation of patients eligible for treatment

- a) Adult patients with previously untreated chronic lymphocytic leukaemia, eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)  
approx. 1810 patients
- b) Adult patients with previously untreated chronic lymphocytic leukaemia, not eligible for therapy with FCR  
approx. 810 patients
- c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons  
approx. 470 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: 29 January 2021):

[https://www.ema.europa.eu/documents/product-information/imbruvica-epar-product-information\\_de.pdf](https://www.ema.europa.eu/documents/product-information/imbruvica-epar-product-information_de.pdf)

Treatment with ibrutinib combined with rituximab 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:

- a) Adult patients with previously untreated chronic lymphocytic leukaemia, eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ibrutinib	€ 75.227.15
Rituximab	€ 19.800.06
additionally required SHI services	€ 68.95
Total:	€ 95.096.16
Appropriate comparator therapy:	
Fludarabin + cyclophosphamide + rituximab (FCR)	
Fludarabine	€ 1.892.40
Cyclophosphamide	€ 213.69
Rituximab	€ 19.800.06
additionally required SHI services	€ 57.55
Total:	€ 21.963.70

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

Other SHI services:

Designation of the 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	€ 1458
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	18	€ 1458
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426

- b) Adult patients with previously untreated chronic lymphocytic leukaemia, not eligible for therapy with FCR

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ibrutinib	€ 75.227.15
Rituximab	€ 19.800.06
additionally required SHI services	€ 68.95
Total:	€ 95.096.16
Appropriate comparator therapy:	
Bendamustine + rituximab (BR)	
Bendamustine	€ 5.261.55
Rituximab	€ 19.800.06
additionally required SHI services	€ 57.55
Total:	€ 25.119.16
Chlorambucil + rituximab (ClbR)	
Chlorambucil	€ 165.70
Rituximab	€ 19.800.06
additionally required SHI services	€ 57.55
Total:	€ 20.023.31
Chlorambucil + obinutuzumab	
Chlorambucil	€ 165.70
Obinutuzumab	€ 27.900.56

Designation of the therapy	Annual treatment costs/patient
additionally required SHI services	€ 144.68
<b>Total:</b>	<b>€ 28.210.94</b>

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

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Bendamustine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	12	€ 972
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426
Obinutuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	Cycle 1: 4 Cycle 2–6: 1	9	€ 639

- c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ibrutinib	€ 75.227.15
Rituximab	€ 19.800.06
additionally required SHI services	€ 68.95
<b>Total:</b>	<b>€ 95.096.16</b>
Appropriate comparator therapy:	
Ibrutinib	
Ibrutinib	€ 75.227.15

Designation of the therapy	Annual treatment costs/patient
additionally required SHI services	€ 11.40
<b>Total:</b>	<b>€ 75.238.55</b>

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

Other SHI services:

Designation of the 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	6	€ 426