Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an amendment to the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V Venetoclax (New therapeutic indication: chronic lymphocytic leukaemia, combination with rituximab)

From 16. May 2019

At its meeting on 16. May 2019, the Federal Joint Committee (G-BA) decided to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive) in the version dated 18 December 2008/22 January 2009 (BAnz. No. 49a of 31 March 2009), as last amended on TT. Monat JJJJ (BAnz AT TT.MM.JJJJ BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Venetoclax in accordance with the Resolution of 16 May 2019:

Venetoclax

Resolution from: 16. May 2019
Entry into force on: 16. May 2019
BAnz. AT TT. MM JJJJ Bx

New therapeutic indication (according to marketing authorisation dated 29 October 2018):

Venclyxto in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

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

a) Adult patients with CLL without 17p deletion or TP53 mutation for whom chemo-immunotherapy is indicated and who have received at least one prior therapy.

Appropriate comparator therapy:

A patient-individualized chemo-immunotherapy with selection of bendamustine, chlorambucil, fludarabine with cyclophosphamide, and ibrutinib with bendamustine, each in combination with rituximab, taking into account the general condition as well as the success and tolerability of the previous therapy.

The extent and probability of additional benefit of Venetoclax in combination with rituximab compared with appropriate comparator therapy:

a1) Patients for whom bendamustine in combination with rituximab is the patient-individually most suitable therapy

Indication of a minor additional benefit.

a2) Patients for whom a therapy other than bendamustine in combination with rituximab is the patient-individually most suitable therapy

An additional benefit is not proven.

b) Adult patients with CLL with 17p deletion or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy

Appropriate comparator therapy:

Ibrutinib

or

Idelalisib + rituximab

or

Best supportive care (only for patients for whom prior therapy with ibrutinib or idelalisib + rituximab failed)

Best supportive care is the therapy that ensures the best possible, individually optimised, supportive treatment to alleviate symptoms and improve the quality of life.

Extent and probability of additional benefit of Venetoclax in combination with rituximab compared with appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adult patients with CLL without 17p deletion or TP53 mutation for whom chemo-immunotherapy is indicated and who have received at least one prior therapy.

a1) Patients for whom bendamustine in combination with rituximab is the patient-individually most suitable therapy

Mortality

Endpoint	**Venetoclax + rituximab**		**Bendamustine + rituximab**		**Intervention vs monitoring**
	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)
Overall survival					
	74	n.a. 4 (5.4)	66	n.a. 10 (15.2)	0.32 [0.10; 1.02]; 0.043[b] AD: n.b.

Morbidity

[1] Data from the IQWiG dossier evaluation (A18-81) and addendum (A19-35) unless otherwise indicated.

Endpoint	Venetoclax + rituximab		Bendamustine + rituximab		Intervention vs Monitoring
	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[c] Absolute difference (AD)
Progression-free survival (PFS)					
IRC assessment DC: 8 May 2017	74	n.a. 7 (9.5)	66	22.8 [16.2; 33.0] 34 (51.5)	0.11 [0.05; 0.25]; < 0.001 AD: n.b.
Health status (EQ-5D VAS)					
Time until improvement by ≥ 7 points[d]	30	11.0 [2.7; n.b.] 19 (63.3)	62	3.0 [1.9; 6.9] 41 (66.1)	0.66 [0.37; 1.16]; 0.142
Time until improvement by ≥ 12 points[d]	30	n.a. [8.3; n.b.] 13 (43.3)	62	15.6 [5.6; n.b.] 30 (48.4)	0.63 [0.33; 1.23]; 0.171
Time until deterioration by ≥ 7 points[d]	30	31.4 [6.8; n.b.] 15 (50.0)	62	12.4 [4.7; 25.6] 37 (59.7)	0.66 [0.36; 1.23]; 0.186
Time until deterioration by ≥ 12 points[d]	30	n.a. [22.5; n.b.] 11 (36.7)	62	n.a. [21.6; n.b.] 24 (38.7)	0.79 [0.38; 1.67]; 0.542

Endpoint	Venetoclax + rituximab			Bendamustine + Rituximab			Intervention vs Monitoring
	N[e]	Values at the start of the study MV (SD)	Change of EOCTR medical round MV[f] (SE)	N[e]	Values at the start of the study MV (SD)	Change of EOCTR medical round MV[f] (SE)	MD [95% CI]; p value[f] Absolute difference (AD)
EQ-5D VAS[g]	n.s.	75.17 (17.57)	9.21 (2.53)	n.s.	70.29 (19.51)	3.67 (1.78)	5.54 [−0.54; 11.63]; 0.074
Symptom scales (EORTC QLQ-C30)[h]							
Fatigue	n. s.	26.67 (23.63)	−8.16 (3.55)	n. s.	34.05 (24.63)	−8.21 (2.51)	0.04 [−8.50; 8.59]; 0.992

Endpoint	Venetoclax + rituximab			Bendamustine + Rituximab			Intervention vs Monitoring
	N[e]	Values at the start of the study MV (SD)	Change of EOCTR medical round MV[f] (SE)	N[e]	Values at the start of the study MV (SD)	Change of EOCTR medical round MV[f] (SE)	MD [95% CI]; p value[f] Absolute difference (AD)
Nausea/vomiting	n. s.	1.11 (4.23)	−0.52 (1.85)	n. s.	6.18 (14.23)	−1.56 (1.31)	1.05 [−3.42; 5.52]; 0.646
Pain	n. s.	7.78 (14.34)	−0.46 (2.60)	n. s.	13.17 (21.58)	−1.10 (1.84)	0.64 [−5.61; 6.89]; 0.841
Dyspnoea	n. s.	16.67 (24.37)	−10.80 (4.11)	n. s.	22.04 (26.95)	−6.68 (2.90)	-4.12 [−14.00; 5.76]; 0.413
Insomnia	n. s.	18.89 (20.87)	−4.58 (5.02)	n. s.	28.96 (29.49)	3.91 (3.58)	-8.49 [−20.60; 3.62]; 0.169
Loss of appetite	n. s.	3.33 (10.17)	−7.56 (3.76)	n. s.	20.97 (27.15)	−1.65 (2.67)	-5.92 [−15.00; 3.17]; 0.202
Constipation	n. s.	3.33 (10.17)	0.38 (3.45)	n. s.	11.48 (21.85)	−0.81 (2.45)	1.19 [−7.13; 9.51]; 0.779
Diarrhoea	n.s.	4.44 (11.52)	12.64 (3.87)	n.s.	13.89 (23.20)	1.91 (2.77)	10.74 [1.37; 20.10]; 0.025 Hedges' g [95%-CI][i]: 0.50 [0.05; 0.94]

(Continuation)

Health related quality of life

Endpoint	Venetoclax + rituximab			Bendamustine + rituximab			Intervention vs Monitoring
	N[e]	Values at the start of the study MV (SD)	Change of EOCTR medical round MV[f] (SE)	N[e]	Values at the start of the study MV (SD)	Change of EOCTR medical round MV[f] (SE)	MD [95% CI]; p value[f] Absolute difference (AD)
Functional scales (EORTC QLQ-C30)[h]							
General health status	n. s.	71.11 (19.42)	9.48 (3.56)	n. s.	64.62 (20.62)	2.85 (2.52)	6.63 [−1.94; 15.19]; 0.129
Bodily function	n. s.	87.78 (15.17)	2.07 (2.24)	n. s.	84.81 (17.15)	0.92 (1.58)	1.15 [−4.23; 6.53]; 0.674

Endpoint	Venetoclax + rituximab			Bendamustine + rituximab			Intervention vs Monitoring
	N[e]	Values at the start of the study MV (SD)	Change of EOCTR medical round MV[f] (SE)	N[e]	Values at the start of the study MV (SD)	Change of EOCTR medical round MV[f] (SE)	MD [95% CI]; p value[f] Absolute difference (AD)
Role function	n. s.	87.78 (19.04)	4.75 (3.52)	n. s.	79.03 (25.24)	2.62 (2.49)	2.13 [−6.34; 10.61]; 0.622
Cognitive function	n. s.	90.00 (16.14)	1.48 (3.55)	n. s.	87.43 (16.00)	−3.31 (2.51)	4.79 [−3.75; 13.34]; 0.271
Emotional function	n. s.	81.11 (18.82)	7.49 (2.83)	n. s.	80.87 (21.37)	2.19 (2.00)	5.30 [−1.50; 12.11]; 0.126
Social function	n. s.	90.56 (16.77)	2.53 (3.31)	n. s.	85.52 (21.83)	−0.80 (2.34)	3.34 [−4.62; 11.30]; 0.411

(Continuation)

Side effects

Endpoint	Venetoclax + rituximab		Bendamustine + rituximab		Intervention vs Monitoring
	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)
Total adverse events (presented additionally)					
	74	0.3 [0.1; 0.5] 74 (100)	66	0.1 [0.0; 0.3] 64 (97.0)	-
Serious adverse events (SAE)					
	74	n.a. [25.0; n.b.] 28 (37.8)	66	8.8 [8.8; 21.8] 25 (37.9)	0.39 [0.20; 0.76]; 0.005
Severe adverse events (CTCAE grade 3 or 4)[j]					
	74	3.1 [1.4; 6.7] 59 (79.7)	66	3.7 [2.1; 10.3] 43 (65.2)	1.04 [0.69; 1.57]; 0.847
Treatment withdrawals because of adverse events[j]					
	74	n.a. 12 (16.2)[k]	66	n.a. 7 (10.6)	0.36 [0.09; 1.40]; 0.125
Specific adverse events					
Nausea (PT, AE)	74	n.a. 13 (17.6)	66	n.a. [2.3; n.b.] 27 (40.9)	0.29

Endpoint	Venetoclax + rituximab		Bendamustine + rituximab		Intervention vs Monitoring
	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)
					[0.14; 0.59]; < 0.001
Vomiting (PT, AE)	74	n.a. 7 (9.5)	66	n.a. 11 (16.7)	0.30 [0.10; 0.95]; 0.041
Infusion-related reaction (PT, AE)	74	n.a. 6 (8.1)	66	n.a. 17 (25.8)	0.29 [0.12; 0.74]; 0.009
Reduced appetite (PT, AE)	74	n.a. 2 (2.7)	66	n.a. 7 (10.6)	0.12 [0.01; 0.96]; 0.046
Dyspnoea (PT, AE)	74	n.a. 2 (2.7)	66	n.a. 8 (12.1)	0.10 [0.01; 0.83]; 0.033
Rash (PT, AE)	74	n.a. 7 (9.5)	66	n.a. [8.8; n.b.] 9 (13.6)	0.17 [0.04; 0.70]; 0.014
Infections and parasitic diseases (SOC, SAE)	74	n.a. 13 (17.6)	66	n.a. [8.8; n.b.] 12 (18.2)	0.33 [0.12; 0.94]; 0.038

a: HR and CI: Cox Proportional Hazards Model, p value: Log Rank Test; for endpoint overall survival (model and test), stratified by geographic region; for the endpoints of the category side effects (model and test), unstratified
b: Discrepancy between the results of the stratified log-rank test and the Cox proportional hazards model (p = 0.054).
c: HR and CI: Cox Proportional Hazards Model, p value: Log-rank test; stratified by geographical region in each case
d: Change compared to baseline value; operationalisation not pre-specified
e: Number of patients included in the evaluation to calculate the effect estimation. Values at the beginning of the study may be based on different patient numbers.
f: mean and SE (change in EOCTR medical round per treatment group) as well as MD, 95% CI, and p value (group comparison): MMRM; adjusted for value at the beginning of the study
g: Positive values mean an improvement.
h: In the symptom scales, low values mean a better symptomatology (negative change: improvement); for health-related quality of life, high values mean a higher quality of life (positive change: improvement)
i: IQWiG calculation based on MD and CI estimates of MMRM under the assumption that all patients with baseline values (30 [venetoclax + rituximab] vs 60 [bendamustine + rituximab]) were included in the evaluation.
j: Also contains events that can be assigned to the progression of the underlying disease.
k: Events occurred in 9 patients during the dosing phase and in 3 patients during the combination therapy phase.

Abbreviations used:

AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; DC = data cut-off; EOCTR: End of Combination Treatment Response; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: European Quality

Endpoint	Venetoclax + rituximab		Bendamustine + rituximab		Intervention vs Monitoring
	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)
of Life Questionnaire – 5 Dimensions; HR = Hazard Ratio; IRC = Independent Review Committee; n.s: not specified; CI = confidence interval; MD: Mean difference; MMRM: mixed model with repeated measurements; M: mean; N = number of patients assessed; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT: preferred term; SD: standard deviation; SE: standard error; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus					

a2) Patients for whom a therapy other than bendamustine in combination with rituximab is the patient-individually most suitable therapy

There is no data that would allow for the assessment of the additional benefit.

b) Adult patients with CLL with 17p deletion or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy

There is no data that would allow for the assessment of the additional benefit.

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

a) Adult patients with CLL without 17p deletion or TP53 mutation for whom chemo-immunotherapy is indicated and who have received at least one prior therapy.

Approx. 1500–5600 patients

b) Adult patients with CLL with 17p deletion or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy

Approx. 500–1900 patients

3. Requirements for quality-assured application

The requirements of the product information must be taken into account. The European Medicines Agency (EMA) makes the contents of the summary of product characteristics on Venclyxto® (active ingredient: Venetoclax) freely available under the following link (last access: 2. April 2019):

https://www.ema.europa.eu/documents/product-information/venclyxto-epar-product-information_de.pdf

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

4. Treatment costs

Annual treatment costs:

a) Adult patients with CLL without 17p deletion or TP53 mutation for whom chemo-immunotherapy is indicated and who have received at least one prior therapy.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Venetoclax + rituximab	
Venetoclax	€ 80,022.20[2]
Rituximab	€ 19,799.28
Total	€ 99,821.48
Appropriate comparator therapy[3]:	
Bendamustine + rituximab (BR)	
Bendamustine	€ 5,331.90
Rituximab	€ 19,799.28
Total	€ 25,131.18
Chlorambucil + rituximab (ClbR)	
Chlorambucil	€ 337.10
Rituximab	€ 19,799.28
Total	€ 20,136.38
Fludarabine + cyclophosphamide + rituximab (FCR)	
Fludarabine	€ 1,892.04
Cyclophosphamide	€ 213.51
Rituximab	€ 19,799.28

[2] Taking into account the initial 5-week dosage, which does not apply to subsequent years if applied for more than one yearAnnual treatment costs in subsequent years: € 85,010.59

[3] Exemplary representation of some common therapy schemes.

Designation of the therapy	Annual treatment costs/patient
Total	€ 21,904.83
Ibrutinib + bendamustine + rituximab (IbrBR)	
Ibrutinib	€ 77,696.09
Bendamustine	€ 5,331.90
Rituximab	€ 19,799.28
Total	102,827.27

Costs after deduction of statutory discounts (Lauer-Taxe® as last revised: 15. April 2019)

Costs for additional SHI services required: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year	Cost per patient per year
Medicinal product to be assessed					
Venetoclax + rituximab					
Rituximab	Supplement for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426
Appropriate comparator therapy					
Bendamustine + rituximab (BR)					
Bendamustine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	12	€ 972
Rituximab	Supplement for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426
Total	€ 1,398				
Chlorambucil + rituximab (ClbR)					
Rituximab	Supplement for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426
Fludarabine + cyclophosphamide + rituximab (FCR)					

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year	Cost per patient per year
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	18	€ 1,458
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	18	€ 1,458
Rituximab	Supplement for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426
Total	€ 3,342				
Ibrutinib + bendamustine + rituximab (IbrBR)					
Bendamustine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	12	€ 972
Rituximab	Supplement for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426
Total	€ 1,398				

b) Adult patients with CLL with 17p deletion or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Venetoclax + rituximab	
Venetoclax	€ 80,022.20[4]
Rituximab	€ 19,799.28
Additional SHI services required	*€ 42.28*
Total	€ 99,863.76
Appropriate comparator therapy:	
Ibrutinib	

[4] Taking into account the initial 5-week dosage, which does not apply to subsequent years if applied for more than one year.
Annual treatment costs in subsequent years: € 85,010.59

Designation of the therapy	Annual treatment costs/patient
Total	€ 77,696.09
Idelalisib + rituximab	
Idelalisib	€ 52,040.00
Rituximab	€ 26,507.36
Additional SHI services required	*€ 42.28*
Total	€ 78,589.64
Best supportive care (BSC)[5]	
Total	Different between each individual patient

Costs after deduction of statutory discounts (Lauer-Taxe® as last revised: 15. April 2019)

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year	Cost per patient per year
Medicinal product to be assessed					
Venetoclax + rituximab					
Rituximab	Supplement for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426
Appropriate comparator therapy					
Idelalisib + rituximab					
Rituximab	Supplement for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8	€ 568

II. The resolution will enter into force on the day of its publication on the Internet on the websites of the Federal Joint Committee on 16. May 2019.

The justification to this resolution will be published on the website of the Federal Joint Committee at www.g-ba.de .

Berlin, 16. May 2019

[5] In a comparison with BSC, this should also be used in addition to the medicinal product to be assessed.

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof Hecken