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
Polatuzumab Vedotin (new therapeutic indication: diffuse large B-cell lymphoma (DLBCL), combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP))

of 1 December 2022

At its session on 1 December 2022, 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 Polatuzumab Vedotin in accordance with the resolution of 20 August 2022:

Polatuzumab vedotin

Resolution of: 1 December 2022
Entry into force on: 1 December 2022
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 24 May 2022):

Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

Therapeutic indication of the resolution (resolution of 1 December 2022):

See new therapeutic indication according to marketing authorisation

1. Extent of the additional benefit and significance of the evidence

Polatuzumab vedotin is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

<u>Adults with previously untreated diffuse large B-cell lymphoma (DLBCL)</u>

Extent of additional benefit and significance of the evidence of polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Adults with previously untreated diffuse large B-cell lymphoma (DLBCL)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences 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	↔	No relevant difference 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 ↓↓: 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.c.: not calculable		

- POLARIX study: multicentre, double-blind, placebo-controlled RCT; polatuzumab vedotin + rituximab + cyclophosphamide + doxorubicin + prednisone (Pola + R-CHP) vs rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP); data cut-off from 15 June 2022

Mortality

Endpoint	Pola+R-CHP		R-CHOP		Pola+R-CHP vs R-CHOP
	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[a)] [95% CI] p value
Overall survival					
	440	n.a. [n.a.; n.a.] 64 (14.5)	439	n.a. [n.a.; n.a.] 67 (15.3)	0.94 [0.67; 1.34] 0.733

[1] Data from the amendment of the G-BA (published on 1. Dezember 2022), unless otherwise indicated.

Morbidity

Endpoint	Pola+R-CHP		R-CHOP		Pola+R-CHP vs R-CHOP
	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[a)] [95% CI] p value
Progression-free survival (PFS)[2]					
	440	n.a. [n.a.; n.a.] *118 (26.8)*	439	n.a. [n.a.; n.a.] *143 (32.6)*	0.76 [0.60; 0.97] *0.030*
Disease progression		96 (21.8)		122 (27.8)	
Death		22 (5.0)		21 (4.8)	
Event-free survival (EFS)					
	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[a)] [95% CI] p value
	440	n.a. [n.a.; n.a.] *124 (28.2)*	439	n.a. [n.a.; n.a.] *147 (33.5)*	0.785 [0.617; 0.999] 0.048
Disease progression/ recurrences		93 (21.1)		112 (25.5)	
Death		21 (4.8)		21 (4.8)	
NALT for effectiveness reasons[b)]		9 (2.0)		8 (1.8)	
Residual disease (biopsy)		1 (0.2)		6 (1.4)	

[2] Data from the amendment of the G-BA (published on 1. December 2022), presented additionally.

Endpoint	Pola+R-CHP		R-CHOP		Pola+R-CHP vs R-CHOP
	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[a)] [95% CI] p value
EORTC QLQ-C30 - Fatigue[3]					
Time to first deterioration					
	440	6.7 [2.9; 24.3] *223 (50.7)*	439	3.0 [2.8; 6.8] *230 (52.4)*	0.94 [0.78; 1.13] n.d.

[3] Data from the G-BA's dossier assessment (published on 1 September 2022), based on the data cut-off of 28 June 2021.

Endpoint	Pola+R-CHP				R-CHOP				Pola+R-CHP vs R-CHOP
	N	Base-line MV (SD)	N	End of treatment/ premature discontinuation *Change from baseline LS mean[d] (SE)*	N	Base-line MV (SD)	N	End of treatment/ premature discontinuation *Change from baseline LS mean[d] (SE)*	LS mean difference[d] [95% CI] p value
Disease symptomatology[3] (EORTC QLQ-C30)[c)]									
Fatigue	417	37.66 (27.41)	385	-10.49 (1.07)	410	35.22 (27.01)	364	-7.96 (1.09)	-2.53 [-5.53; 0.46] n.d.
Pain	417	31.14 (31.20)	386	-10.58 (1.23)	410	27.85 (30.60)	367	-11.30 (1.25)	0.72 [-2.73; 4.16] n.d.
Nausea/ vomiting	417	8.43 (18.57)	385	-4.14 (0.50)	410	6.14 (14.59)	365	-3.95 (0.51)	-0.19 [-1.60; 1.22] n.d.
Dyspnoea	417	19.42 (27.99)	385	-2.91 (1.07)	409	16.46 (26.00)	365	-5.18 (1.09)	2.26 [-0.74; 5.27] n.d.
Appetite loss	417	27.34 (34.18)	384	-14.98 (0.97)	410	24.80 (33.13)	364	-16.52 (0.99)	1.53 [-1.19; 4.26] n.d.
Insomnia	416	37.18 (34.11)	385	-15.52 (1.29)	409	36.84 (34.00)	364	-16.06 (1.32)	-0.54 [-3.07; 4.15] n.d.
Constipation	411	21.33 (30.56)	380	-11.11 (0.96)	404	21.86 (29.48)	357	-12.31 (0.98)	1.20 [-1.49; 3.89] n.d.
Diarrhoea	413	10.33 (21.43)	378	-1.93 (0.88)	406	9.20 (19.68)	363	-2.70 (0.90)	0.77 [-1.69; 3.23] n.d.
Neurotoxicity[3] (FACT/GOG-NTX)[e]									
	412	39.75 (4.50)	384	-2.96 (0.32)	407	39.48 (4.99)	375	-1.90 (0.32)	-1.06 [-1.94; -0.18] n.d.
General health status[3] (EQ-5D-VAS)[f]									
	405	68.74 (21.65)	370	9.39 (0.78)	406	69.97 (19.84)	358	10.36 (0.78)	-0.96 [-3.13; 1.20] n.d.

Health-related quality of life

Endpoint	Pola+R-CHP		R-CHOP		Pola+R-CHP vs R-CHOP
	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[a)] [95% CI] p value
EORTC QLQ-C30 – Physical functioning[3]					
Time to first deterioration					
	440	n.a. [18.9; n.a.] *183 (41.6)*	439	25.5 [17.6; n.a.] *187 (42.6)*	0.97 [0.79; 1.19] n.d.

Endpoint	Pola+R-CHP				R-CHOP				Pola+R-CHP vs R-CHOP
	N	Baseline MV (SD)	N	End of treatment/ premature discontinuation *Change from baseline LS mean[d)] (SE)*	N	Baseline MV (SD)	N	End of treatment/ premature discontinuation *Change from baseline LS mean[d)] (SE)*	LS mean difference[d)] [95% CI] p value
Health-related quality of life[3] (EORTC QLQ C-30)[g)]									
Global health status/ Global quality of life	414	59.68 (24.58)	381	11.18 (0.97)	406	61.99 (23.90)	363	12.22 (0.98)	-1.04 [-3.74; 1.67] n.d.
Physical functioning	416	79.71 (22.31)	385	2.69 (0.89)	410	80.35 (22.68)	365	3.90 (0.90)	-1.22 [-3.70; 1.27] n.d.
Role functioning	416	68.95 (33.92)	384	9.16 (1.21)	410	71.22 (32.06)	365	10.58 (1.23)	-1.42 [-4.82; 1.97] n.d.
Emotional functioning	415	75.68 (21.95)	382	9.05 (0.84)	407	73.64 (22.42)	364	8.87 (0.86)	0.18 [-2.18; 2.54] n.d.

Endpoint	Pola+R-CHP				R-CHOP				Pola+R-CHP vs R-CHOP
	N	Baseline MV (SD)	N	End of treatment/ premature discontinuation *Change from baseline LS mean[d] (SE)*	N	Baseline MV (SD)	N	End of treatment/ premature discontinuation *Change from baseline LS mean[d] (SE)*	LS mean difference[d] [95% CI] p value
Cognitive functioning	415	84.82 (20.49)	382	0.93 (0.85)	406	86.45 (18.14)	363	0.13 (0.87)	0.80 [-1.59; 3.18] n.d.
Social functioning	415	73.90 (29.30)	381	7.68 (1.14)	405	74.77 (28.08)	362	9.25 (1.17)	-1.57 [-4.77; 1.64] n.d.
Health-related quality of life[3] (FACT-LymS)[h]									
	410	44.55 (9.96)	377	6.73 (0.35)	405	45.23 (9.97)	359	6.22 (0.36)	0.51 [-0.48; 1.50] n.d.

Side effects[3]

Endpoint	Pola+R-CHP		R-CHOP		Pola+R-CHP vs R-CHOP
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[i)]
Adverse events in total					
	435	426 (97.9)	438	431 (98.4)	-
Serious adverse events (SAE)					
	435	148 (34.0)	438	134 (30.6)	1.11 [0.92; 1.35] 0.279
Severe adverse events (CTCAE grade 3 or 4)					
	435	264 (60.7)	438	262 (59.8)	1.01 [0.91; 1.13] 0.792
Therapy discontinuation due to adverse events					
AE that led to discontinuation of at least one component of the study medication[j)]	435	27 (6.2)	438	29 (6.6)	0.94 [0.56; 1.56] 0.803
AE that led to discontinuation of polatuzumab vedotin/ placebo or vincristine/ placebo[j)]	435	19 (4.4)	438	22 (5.0)	n.d.
Severe AEs (CTCAE grade ≥ 3) with incidence ≥ 5% at SOC level					
Blood and lymphatic system disorders					
	435	183 (42.1)	438	174 (39.7)	1.06 [0.90; 1.24] 0.482
Gastrointestinal disorders					
	435	42 (9.7)	438	36 (8.2)	1.17 [0.77; 1.80] 0.458
General disorders and administration site conditions					
	435	29 (6.7)	438	25 (5.7)	1.17 [0.70; 1.96]; 0.557
Infections and infestations[k)]					
	435	66 (15.2)	438	55 (12.6)	1.21 [0.87; 1.68] 0.265

Endpoint	Pola+R-CHP		R-CHOP		Pola+R-CHP vs R-CHOP
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[i)]
Investigations					
	435	59 (13.6)	438	60 (13.7)	0.99 [0.71; 1.38] 0.954
Metabolism and nutrition disorders					
	435	40 (9.2)	438	34 (7.8)	1.18 [0.76; 1.83] 0.448
Serious AEs (SAEs) with incidence ≥ 5% according to SOC and PT					
Blood and lymphatic system disorders					
	435	50 (11.5)	438	40 (9.1)	1.26 [0.85; 1.87] 0.253
Febrile neutropenia					
	435	43 (9.9)	438	28 (6.4)	1.55 [0.98; 2.44] 0.062
Gastrointestinal disorders					
	435	31 (7.1)	438	26 (5.9)	1.20 [0.73; 1.99] 0.477
General disorders and administration site conditions					
	435	26 (6.0)	438	20 (4.6)	1.31 [0.74; 2.31] 0.353
Infections and infestations[k)]					
	435	61 (14.0)	438	45 (10.3)	1.36 [0.95; 1.96] 0.092
AEs of special interest					
Drug-induced liver damage					
All severity grades	435	1 (0.2)	438	2 (0.5)	0.50 [0.05; 5.53] 0.575
Severity grade ≥ 3	435	1 (0.2)	438	2 (0.5)	0.50 [0.05; 5.53] 0.575
SAE	435	0	438	1 (0.2)	-
Suspicion of transmission of an infectious agent by the study medication					
	435	0	438	0	-

Sensory and/or motor peripheral neuropathy					
All severity grades	435	230 (52.9)	438	236 (53.9)	0.98 [0.87; 1.11] 0.765
Severity grade ≥ 3	435	7 (1.6)	438	5 (1.1)	1.41 [0.45; 4.41] 0.555
SAE	435	1 (0.2)	438	1 (0.2)	1.01 [0.06; 16.05] 0.996
Neutropenia, including febrile neutropenia[l)]					
All severity grades	435	200 (46.0)	438	187 (42.7)	1.08 [0.93; 1.25] 0.329
Severity grade ≥ 3	435	182 (41.8)	438	176 (40.2)	1.04 [0.89; 1.22] 0.619
SAE	435	50 (11.5)	438	37 (8.4)	1.36 [0.91; 2.04] 0.135
Hepatic toxicity[l)]					
All severity grades	435	46 (10.6)	438	32 (7.3)	1.45 [0.94; 2.23] 0.093
Severity grade ≥ 3	435	8 (1.8)	438	4 (0.9)	2.01 [0.61; 6.64] 0.250
SAE	435	1 (0.2)	438	0	-

a) Cox proportional hazards model stratified by IPI score (2 vs 3-5), bulky disease defined as a lesion ≥ 7.5 cm (present vs absent), geographic region (Western Europe, USA, Canada, Australia vs Asia vs rest of the world). p value based on two-sided stratified log-rank test.
b) The date of the EFS event is the date of the test or biopsy whose finding results in a NALT, not the date of the start of the NALT.
c) Scale 0–100. Lower (decreasing) values mean better symptomatology; negative effects (intervention – control) mean an advantage for the intervention.
d) MMRM model with treatment, study visit, interaction term treatment x study visit and baseline value as covariates.
e) Scale 0–44. Lower (decreasing) values mean improvement in symptomatology (neuropathy), negative effects (intervention – control) mean an advantage for the intervention. The clinical relevance of the effect cannot be assessed due to the lack of Hedges' g information.
f) Scale 0–100. Higher (increasing) values mean improvement.
g) Scale 0–100. Higher (increasing) values mean better health status / better quality of life, positive effects (intervention – control) mean an advantage for the intervention.
h) Scale 0–60. Higher (increasing) values mean better quality of life.
i) Unstratified analysis; p value based on Wald test.
j) Study participants essentially received the study medication until the occurrence of disease progression, initiation of other antineoplastic therapy or the occurrence of certain AEs, whichever came first. Disease progression and subsequent therapies that may occur prior to potential discontinuation due to AEs represent a competing event, which is why the reliability and interpretability of the result is limited.

k) Defined as AE of special interest.
l) Defined as "select AE".

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; EQ-5D-VAS: European Quality of Life 5 Dimension Visual Analogue Scale; FACT/GOG-NTX: Functional Assessment of Cancer Therapy/ Gynaecologic Oncology Group - Neurotoxicity; FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale; HR = hazard ratio; IPI = International Prognostic Index; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; NALT = new anti-lymphoma therapy; n.a. = not achieved; R-CHOP: rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; Pola+R-CHP: polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone; SD: standard deviation; SE: standard error; (S)AE = (serious) adverse event; vs = versus.

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

Adults with previously untreated diffuse large B-cell lymphoma (DLBCL)

approx. 5,510 - 6,130 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 Polivy (active ingredient: polatuzumab vedotin) at the following publicly accessible link (last access: 22 August 2022):

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

Treatment with polatuzumab vedotin should only be initiated and monitored by specialists in internal medicine, haematology and oncology, experienced in the treatment of patients with diffuse large B-cell lymphoma (DLBCL).

Data on the safety and efficacy of polatuzumab vedotin are not available for patients with an International Prognostic Index (IPI) of 0-1.

This medicinal product was authorised under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL)

Designation of the therapy	Annual treatment costs/ patient
Polatuzumab vedotin	€ 71,425.56
Cyclophosphamide	€ 192.60
Doxorubicin	€ 1,531.36
Prednisone	€ 82.21
Rituximab	€ 21,713.72
Total	€ 94,945.45
Additionally required SHI services:	€ 77.65

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 November 2022)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Polatuzumab vedotin	Surcharge for production	€ 100	1	6	€ 600
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	6	€ 600

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Doxorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	6	€ 600
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	8	€ 800

5. Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Polatuzumab Vedotin

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 polatuzumab vedotin for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) on the basis of the marketing authorisation granted under Medicinal Products Act:

Adults with previously untreated diffuse large B-cell lymphoma (DLBCL)

- *No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.*

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 1 December 2022.

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

Berlin, 1 December 2022

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

Prof. Hecken