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 (reassessment of an orphan drug > EUR 30 million turnover limit: diffuse large B-cell lymphoma (DLBCL), combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP); first-line)

of 20 June 2024

At its session on 20 June 2024, 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 Polatuzumab vedotin in accordance with the resolution of 20 June 2024 on the therapeutic indication "for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant":**

Polatuzumab vedotin

Resolution of: 20 June 2024
Entry into force on: 20 June 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

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 20 June 2024):

See therapeutic indication according to marketing authorisation.

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

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

Appropriate comparator therapy:

- Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)

Extent and probability of the additional benefit of polatuzumab vedotin in combination with rituximab, cyclophosphamide and doxorubicin compared with the appropriate comparator therapy:

An additional benefit is not proven.

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 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	↔	No relevant difference for the benefit assessment. In detail, disadvantages for the specific AEs "febrile neutropenia" and "diarrhoea".
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		

- POLARIX study: multicentre, double-blind 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 (final analysis of overall survival)

[1] Data from the dossier assessment of the IQWiG (A23-141) and from the addendum (A24-60), unless otherwise indicated.

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 [95% CI] p value[a]
Overall survival					
	500	n.r. 69 (13.8)	500	n.r. 77 (15.4)	0.88 [0.64; 1.22]; 0.450[b]

Morbidity

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 [95% CI] p value[a]
Progression-free survival (PFS)[2]					
PFS	500	n.r. [n.r.; n.r.] 133 (26.6)	500	n.r. [n.r.; n.r.] 163 (32.6)	0.76 [0.60; 0.95] 0.0176
Time to progression/ relapse	500	n.r. [n.r.; n.r.] 110 (22.0)	500	n.r. [n.r.; n.r.] 138 (27.6)	0.74 [0.57; 0.95] 0.0181
Time until death	500	n.r. [n.r.; n.r.] 23 (4.6)	500	n.r. [n.r.; n.r.] 25 (5.0)	0.86 [0.49; 1.52] 0.6031

[2] Data from the dossier of the pharmaceutical company (Module 4 A) of 18.12.2023.

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 [95% CI] p value[a]
Failure of the curative therapeutic approach: Event-Free Survival – End of Treatment (EFS-EOT)					
Event rate[c]	500	– 169 (33.8)	500	– 199 (39.8)	0.85 [0.72; 1.00]; 0.051
Death	500	– 19 (3.8)	500	– 21 (4.2)	–[d]
Progression/ relapse	500	– 95 (19.0)	500	– 123 (24.6)	–[d]
CR not reached at the end of treatment	500	– 55 (11.0)	500	– 55 (11.0)	–[d]
Event-free survival (EFS)	500	n.r. 169 (33.8)	500	n.r. 199 (39.8)	HR: 0.80 [0.65; 0.98]; 0.030[b]

Endpoint	Pola + R-CHP			R-CHOP			Pola + R-CHP vs R-CHOP
	N[e]	Values at start of study MV (SD)	Change at FU month 24 MV[f] (SE)	N[e]	Values at start of study MV (SD)	Change at FU month 24 MV[f] (SE)	MD[f] [95% CI]; p-value
Symptomatology (EORTC QLQ-C30)[g]							
Fatigue	n.d.	35.70 (27.24)	-14.78 (1.13)	n.d.	33.79 (26.47)	-14.82 (1.18)	0.05 [-2.97; 3.07]; 0.976
Nausea and vomiting	n.d.	7.95 (17.78)	-3.66 (0.54)	n.d.	5.85 (14.25)	-4.78 (0.57)	1.12 [-0.35; 2.59]; 0.135
Pain	n.d.	29.38 (30.36)	-12.35 (1.27)	n.d.	27.66 (30.41)	-16.07 (1.32)	3.71 [0.27; 7.15]; 0.034 SMD: 0.19 [0.01; 0.36]
Dyspnoea	n.d.	17.93 (27.03)	-5.34 (1.15)	n.d.	15.71 (25.27)	-2.82 (1.21)	-2.53 [-5.65; 0.59]; 0.112
Insomnia	n.d.	34.67 (33.48)	-17.64 (1.46)	n.d.	34.90 (33.37)	-16.82 (1.53)	-0.82 [-4.78; 3.14]; 0.686
Appetite loss	n.d.	25.00 (32.99)	-16.93 (0.84)	n.d.	23.62 (32.10)	-17.08 (0.89)	0.15 [-2.14; 2.44]; 0.898
Constipation	n.d.	19.79 (29.50)	-9.68 (1.13)	n.d.	20.55 (28.64)	-12.53 (1.18)	2.84 [-0.22; 5.91]; 0.069
Diarrhoea	n.d.	9.53 (20.63)	-2.11 (1.00)	n.d.	8.51 (18.84)	-0.40 (1.06)	-1.71 [-4.48; 1.06]; 0.225
Symptomatology (FACT-LymS[h])							
	n.d.	45.24 (9.94)	7.42 (0.39)	n.d.	45.56 (9.85)	7.29 (0.40)	0.14 [-0.90; 1.18]; 0.796
Symptomatology (FACT/GOG-NtxS[i])							
	n.d.	39.93 (4.46)	-1.45 (0.33)	n.d.	39.63 (4.89)	-1.31 (0.35)	-0.14 [-1.06; 0.77]; 0.759
Health status (EQ-5D VAS[j])							
	n.d.	69.40 (21.53)	10.91 (0.86)	n.d.	70.60 (19.40)	12.21 (0.87)	-1.30 [-3.55; 0.95]; 0.258

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 (%)*	HR [95% CI]; p value[k]
B symptoms[l]	485	n.r. 68 (14.0)	490	n.r. 59 (12.0)	1.15 [0.81; 1.63]; 0.432

Health-related quality of life

Endpoint	Pola + R-CHP			R-CHOP			Pola + R-CHP vs R-CHOP
	N[e]	Values at start of study MV (SD)	Change at FU month 24 MV[f] (SE)	N[e]	Values at start of study MV (SD)	Change at FU month 24 MV[f] (SE)	MD[f] [95% CI]; p-value
EORTC QLQ-C30[j]							
Global health status	n.d.	60.13 (24.54)	15.45 (1.07)	n.d.	62.09 (23.97)	15.31 (1.13)	0.15 [-2.76; 3.06]; 0.920
Physical functioning	n.d.	80.39 (21.96)	5.14 (0.90)	n.d.	80.68 (22.50)	6.31 (0.93)	-1.18 [-3.56; 1.20]; 0.332
Role functioning	n.d.	70.98 (33.22)	15.60 (1.21)	n.d.	72.06 (31.61)	15.85 (1.26)	-0.26 [-3.50; 2.98]; 0.876
Emotional functioning	n.d.	76.81 (21.56)	10.35 (0.95)	n.d.	74.92 (21.84)	12.45 (1.00)	-2.10 [-4.67; 0.47]; 0.110
Cognitive functioning	n.d.	85.34 (20.04)	0.50 (0.95)	n.d.	86.80 (17.67)	1.75 (1.00)	-1.25 [-3.84; 1.34]; 0.345
Social functioning	n.d.	74.58 (28.63)	14.07 (1.10)	n.d.	74.30 (27.70)	16.43 (1.16)	-2.35 [-5.30; 0.59]; 0.117

Side effects[m]

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 (%)*	Relative risk [95% CI] p value
Adverse events in total					
	495	– 485 (98.0)	498	– 491 (98.6)	-
Serious adverse events (SAE)					
	495	– 170 (34.3)	498	– 155 (31.1)	1.10 [0.92; 1.32]; 0.292
Severe adverse events (CTCAE grade 3 or 4)					
	495	– 310 (62.6)	498	– 302 (60.6)	1.03 [0.94; 1.14]; 0.542
Therapy discontinuation due to adverse events					
	495	– 30 (6.1)	498	– 30 (6.0)	1.01 [0.62; 1.64]; > 0.999
Specific adverse events					
Peripheral neuropathy	Evaluations unsuitable[n]				
Infusion-related reactions	Evaluation unsuitable[o]				
Infections and infestations (SOC, severe AEs[p])	495	– 76 (15.4)	498	– 66 (13.3)	1.16 [0.85; 1.57]; 0.530

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 (%)*	Relative risk [95% CI] p value
Other specific AEs					
Febrile neutropenia (PT, severe AEs[p])	495	– 64 (12.9)	498	– 38 (7.6)	1.69 [1.16; 2.48]; 0.006
Diarrhoea (PT, severe AEs[p])	495	– 18 (3.6)	498	– 8 (1.6)	2.26 [0.99; 5.16]; 0.047

a. IQWiG calculations: RR, CI (asymptotic) and p value (unconditional exact test, CSZ method according to Martin Andrés/ Silva Mato. Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods.
b. HR and CI: Cox regression model, stratified by IPI (2 vs 3-5), bulky disease (present vs absent) and geographic region (USA, Western Europe, Canada and Australia vs Asia vs rest of the world). p value from log-rank test.
c. Percentage of patients with a qualifying event for the EFS. The individual components are shown in the lines below.
d. The effect estimators for the individual components are not shown since only the qualifying events for the EFS are specified for the individual components.
e. In the intervention arm vs comparator arm, at least 441 (88.2%) vs 442 (88.4%) patients are included in each case in the effect estimate; the values at the start of study are based on other patient numbers.
f. MMRM evaluation of the ITT population adjusted for the value at the start of study and the stratification factors (IPI [2 vs 3-5], bulky disease [present vs absent] and geographic region [USA, Western Europe, Canada and Australia vs Asia vs rest of the world].
g. Lower (decreasing) values mean better symptomatology; negative effects (intervention minus comparison) mean an advantage for the intervention (scale range 0 to 100).
h. According to the information provided by the pharmaceutical company, higher (increasing) values mean better symptomatology; positive effects (intervention minus comparison) mean an advantage for the intervention (scale range 0 to 60).
i. According to the information provided by the pharmaceutical company, lower (decreasing) values mean better symptomatology; negative effects (intervention minus comparison) mean an advantage for the intervention (scale range 0 to 44).
j. Higher (increasing) values mean a better health status/ better health-related quality of life; positive effects (intervention minus comparison) mean an advantage for the intervention (scale range 0 to 100).
k. HR and CI: Cox regression model, stratified by IPI (2 vs 3-5), bulky disease (present vs absent) and geographic region (USA, Western Europe, Canada and Australia vs Asia vs rest of the world). p value from log-rank test.

l. Operationalised as the time to first occurrence or first recurrence of at least one B-symptom (symptoms collected via eCRF: unexplained fever > 38°C, night sweats with change of clothing, unexplained weight loss > 10% in the last 6 months); no information is available on the percentages at which the symptoms occur
m. Events that occurred in the period from the 1st dose of study medication until 90 days after the last dose of any study medication or until the start of new anti-lymphoma therapy, whichever occurs first
n. No consideration of the preferred terms (PT) of muscle weakness and gait disorder.
o. Although no suitable evaluations are available in the dossier for the endpoint of infusion-related reactions, the events underlying the endpoint are mapped via the specific AEs.
p. Operationalised as CTCAE grade ≥ 3

Abbreviations used:
CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; FACT/GOG-NtxS = Functional Assessment of Cancer Therapy / Gynaecologic Oncology Group - Neurotoxicity Subscale; FACT-LymS = Functional Assessment of Cancer Therapy - Lymphoma Subscale; FU = follow-up; HR = hazard ratio; IPI = International Prognostic Index; ITT = intention to treat; n.d.: no data available; CI = confidence interval; MD: mean difference; MMRM: mixed model with repeated measures; MV: mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.r. = not reached; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire - Core 30; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP = rituximab in combination with cyclophosphamide, doxorubicin and prednisone; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation; SE = standard error; SMD = standardised mean difference; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; 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. 5,640 – 6,270 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: 26 April 2024):

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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Polatuzumab vedotin	€ 64,070.34
In combination with cyclophosphamide + doxorubicin + prednisone + rituximab (R-CHP)	
Cyclophosphamide	€ 192.21
Doxorubicin	€ 1,658.28
Prednisone	€ 81.82
Rituximab	€ 21,709.80
Total	€ 87,712.45
Appropriate comparator therapy:	
Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)	
Cyclophosphamide	€ 287.35
Doxorubicin	€ 2,211.04
Prednisone	€ 91.67
Rituximab	€ 21,709.80
Vincristine	€ 275.28
Total	€ 24,575.14

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2024)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Polatuzumab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	6	€ 600
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	6	€ 600
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
Appropriate comparator therapy:					
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	8	€ 800

Doxorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	8	€ 800
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	8	€ 800
Vincristine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	8	€ 800

5. Designation of 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 the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 June 2024.

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

Berlin, 20 June 2024

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

Prof. Hecken