Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Polatuzumab Vedotin (Diffuse Large B-Cell Lymphoma, Combination with Bendamustine and Rituximab)

of 20 August 2020

At its session on 20 August 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient polatuzumab vedotin as follows:

Polatuzumab vedotin

Resolution of: 20 August 2020
Entry into force on: 20 August 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 16 January 2020):

POLIVY in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

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

Polatuzumab vedotin is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (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>Adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant</u>

Extent of the additional benefit and the significance of the proof for polatuzumab vedotin:

Hint for a non-quantifiable additional benefit because the scientific data does not permit quantification.

Study results according to endpoints:[1]

Adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant

GO29365 study: Polatuzumab vedotin + bendamustine + rituximab (study arm C) **vs** bendamustine + rituximab (study arm D)

Mortality

Endpoint	**Polatuzumab vedotin + bendamustine + rituximab**		**Bendamustine + rituximab**		**Intervention vs control**
	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 (HR) [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	40	12.4 [9.0; 32.0] 26 (65.0)	40	4.7 [3.7; 8.3] 29 (72.5)	0.42 [0.24; 0.73] 0.0014 AD = 7.7 months

Morbidity

Endpoint	**Polatuzumab vedotin + bendamustine + rituximab**		**Bendamustine + rituximab**		**Intervention vs control**
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	relative risk (RR) [95% CI] p value Absolute difference (AD)[a]
Complete response (CR) – presented additionally					
	40	16 (40.0)	40	7 (17.5)	2.29 [1.06; 4.95] 0.036[2] AD = 22.5%

Health-related quality of life

No health-related quality of life data were collected.

[1] Data from the dossier assessment by the G-BA (published on 15 May 2020) and from the amendment (from 10 July 2020) to the dossier assessment unless indicated otherwise.
[2] Data from the dossier on Polatuzumab vedotin (Module 4 A) of 16 January 2020

Side effects

Endpoint	Polatuzumab vedotin + bendamustine + rituximab		Bendamustine + rituximab		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Adverse events in total – presented additionally					
	39	no data available 39 (100)	39	no data available 38 (97.4)	0.70 [0.43; 1.14] 0.1483
Serious adverse events (SAE)					
	39	no data available 26 (66.7)	39	no data available 24 (61.5)	0.62 [0.35; 1.11] 0.1076
Severe adverse events (CTCAE grade ≥ 3)					
	39	no data available 34 (87.2)	39	no data available 29 (74.4)	0.91 [0.54; 1.52] 0.7082
Therapy discontinuation because of adverse events					
	39	no data available 13 (33.3)	39	no data available 5 (12.8)	2.79 [0.98; 7.89] 0.0442
Adverse events of special interest					
Neutropoenia including febrile neutropoenia	39	no data available 25 (64.1)	39	no data available 21 (53.8)	0.95 [0.53; 1.74] 0.8797
Peripheral neuropathy	39	no data available 17 (43.6)	39	no data available 3 (7.7)	5.52 [1.61; 18.86] 0.0022
Infections	39	no data available 21 (53.8)	39	no data available 20 (51.3)	0.58 [0.30; 1.12] 0.0986
Tumour lysis syndrome	39	0	39	0	n.a.
Hepatic toxicity (hyperbilirubinemia, increased transaminase)	39	no data available	39	no data available	1.21 [0.34; 4.33] 0.7666

		7 (17.9)		4 (10.3)	
Genotoxicity/carcinogenicity (myelodysplastic syndrome)	39	no data available 2 (5.1)	39	no data available 2 (5.1)	0.16 [0.01; 1.84] 0.0964
Infusion-related reactions	39	no data available 13 (33.3)	39	no data available 9 (23.1)	1.31 [0.55; 3.10] 0.5455
Hyperglycaemia	39	no data available 1 (2.6)	39	no data available 1 (2.6)	0.99 [0.06; 15.78] 0.9927
Gastrointestinal toxicity (diarrhoea, nausea, vomiting, constipation, anorexia)	39	no data available 32 (82.1)	39	no data available 26 (66.7)	1.10 [0.65; 1.86] 0.7258
Cardiac toxicity and arrhythmias	39	no data available 0	39	no data available 5 (12.8)	< 0.01 [0.00; n.a.] 0.0137
Pharmaceutical interactions	39	0	39	0	n.a.
Immunogenicity (antibodies)	39	no data available	39	no data available	no data available
Reproductive toxicity	39	0	39	0	n.a.
Suspected transmission of an infectious pathogen through the study medication	39	no data available	39	no data available	no data available
Fatigue and asthenia	39	no data available 18 (46.2)	39	no data available 19 (48.7)	0.71 [0.37; 1.36] 0.2944
Anaemia	39	no data available 21 (53.8)	39	no data available 10 (25.6)	1.81 [0.85; 3.86] 0.1203
Thrombocytopoenia	39	no data available 20 (51.3)	39	no data available 13 (33.3)	1.31 [0.65; 2.64] 0.4524
Renal toxicity	39	no data available 4 (10.3)	39	no data available 5 (12.8)	0.44 [0.10; 1.87] 0.2543
Pulmonary toxicity (interstitial lung disease)	39	no data available 2 (5.1)	39	no data available 1 (2.6)	1.50 [0.14; 16.51] 0.7401

Joint pain, arthralgia, skeletal pain	39	no data available 6 (15.4)	39	no data available 1 (2.6)	5.17 [0.62; 43.13] 0.0903
Alopecia	39	no data available 0	39	no data available 1 (2.6)	< 0.01 [0.00; n.a.] 0.2980
Eye toxicity	39	no data available 0	39	no data available 1 (2.6)	< 0.01 [0.00; n.a.] 0.3046
Taste disorders	39	no data available 1 (2.6)	39	no data available 0	> 999.99 [0.00; n.a.] 0.5154
Opportunistic infections	39	no data available 4 (10.3)		no data available 2 (5.1)	no data available

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; RR = relative risk; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	n.a.	No data suitable for the benefit assessment.
Health-related quality of life	∅	No data available.
Side effects	↔	No differences relevant 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.a.: not assessable

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

approx. 730–1,560 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: 9 June 2020):

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

This medicinal product received a conditional marketing authorisation. The EMA 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:

Designation of the therapy	Annual treatment costs/patient
Polatuzumab vedotin	€ 83,331.78
Bendamustine	€ 6,252.60
Rituximab	€ 16,181.10
Additionally required SHI services:	€ 56.11
Total:	€ 105,821.59

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 July 2020

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Polatuzumab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426

Bendamustine	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 81	2	12	€ 972
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 20 August 2020.

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

Berlin, 20 August 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken