Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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: Avelumab (New therapeutic indication: first-line maintenance treatment in adults with locally advanced or metastatic urothelial carcinoma)

of 19 August 2021

At its session on 19 August 2021, 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 on DD. 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 avelumab in accordance with the resolution of 1 October 2020:

Avelumab

Resolution of: 19 August 2021
Entry into force on: 19 August 2021
BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 21 January 2021):

Bavencio is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy.

Therapeutic indication of the resolution (resolution of 19 August 2021):

see therapeutic indication according to marketing authorisation

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

Adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy; first-line maintenance treatment:

Appropriate comparator therapy:

Best supportive care

Extent and probability of the additional benefit of avelumab compared to the best supportive care:

Hint of a considerable additional benefit

Study results according to endpoints:[1]

Adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy; first-line maintenance treatment:

[1] Data from the dossier assessment of the IQWiG (A21-23) and from the addendum (A21-92), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	↓↓	Disadvantages for severe AE and in detail predominantly disadvantages for 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

Study JAVELIN Bladder 100: Avelumab + best supportive care (BSC) **vs** best supportive care

Study design: randomised, controlled, open-label

1. Data cut-off of 21.10.2019

Mortality

Endpoint	Avelumab + BSC		BSC		Intervention vs control
	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 Absolute difference (AD)[a]
overall survival					
1. Data cut-off (21.10.2019)	350	21.4 [18.9; 26.1] *145 (41.4)*	350	14.3 [12.9; 17.9] *179 (51.1)*	0.69 [0.56; 0.86]; 0.001 AD: 7.1 months
Presented additionally:					
2. Data cut-off 90-day safety update (19.01.2020)	350	22.1 [19.0; 26.1] *156 (44.6)*	350	14.6 [12.8; 17.8] *190 (54.3)*	0.70 [0.56; 0.86]; < 0.001 AD: 7.5 months

Morbidity

Endpoint	Avelumab + BSC		BSC		Intervention vs control
	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 Absolute difference (AD)[a]
Progression-free survival (PFS)[b]					
	350	3.7 [3.5; 5.5] *225 (64.3)*	350	2.0 [1.9; 2.7] *260 (74.3)*	0.62 [0.52; 0.75]; < 0.0001 AD: 1.7 months

Endpoint	Avelumab + BSC			BSC			Intervention vs control
	N	Values at the start of the study MV (SD)	Change at time of evaluation MV (SE)	N	Values at the start of the study MV (SD)	Change at time of evaluation MV (SE)	Mean difference [95% CI] p-value Hedges´ g
Symptomatology (NFBISI-18)							
DRS-P	328	27.2 (4.8)	-2.42 [-3.03; -1.82]	319	27.2 (4.8)	-2.89 [-3.60; -2.17]	0.46 [-0.47; 1.40]; 0.329
TSE	328	15.9 (3.1)	-0.79 [-1.13; -0.46]	319	15.8 (2.9)	-0.90 [-1.30; -0.50]	0.11 [-0.42; 0.63]; 0.688
Health status (EQ-5D VAS)							
	331	74.9 (18.9)	-5.21 [-7.29; -3.14]	316	74.9 (16.3)	-7.60 [-10.04; -5.16]	2.39 [-0.81; 5.58]; 0.143

Health-related quality of life

There are no suitable data.

Side effects

Endpoint	Avelumab + BSC		BSC		Intervention vs control
	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 Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	344	0.5 [0.4; 0.5] *338 (98.3)*	345	1.3 [1.0; 1.7] *272 (78.8)*	-
Serious adverse events (SAE)					
	344	28.3 [20.4; n. c.] *114 (33.1)*	345	n. a. [15.2; n. c.] *76 (22.0)*	1.32 [0.98; 1.76]; 0.066
Severe adverse events (CTCAE grade 3 or 4)					
	344	8.8 [6.8; 14.8] *177 (51.5)*	345	18.8 [13.4; n. c.] *101 (29.3)*	1.80 [1.41; 2.30]; < 0.001
Therapy discontinuation due to adverse events					
	No usable data available.				
Specific adverse events					
Immune-mediated AE (presented additionally)	344	4.5 [3.6; 6.4] *206 (59.9)*	345	n. a. [18.9; n. c.] *63 (18.3)*	-
Immune-mediated SAE	344	n.a. *30 (8.7)*	345	n.a. *13 (3.8)*	1.86 [0.97; 3.60]; 0.059
Immune-mediated severe AE	344	n.a. *45 (13.1)*	345	n.a. *16 (4.6)*	2.45 [1.38; 4.35]; 0.002
Infusion-related reactions	No usable data available.				
Hypothyroidism (PT, AE)	344	n.a. *40 (11.6)*	345	n.a. *2 (0.6)*	19.37 [4.68; 80.21] <0.001
Gastrointestinal disorders (SOC, AE)	344	8.2 [6.7; 10.6] *179 (52.0)*	345	24.9 [12.4; n. c.] *102 (29.6)*	1.80 [1.41; 2.30]; < 0.001
Infections and infestations (SOC, AE)	344	7.4 [5.6; 8.7] *186 (54.1)*	345	19.1 [14.0; n. c.] *105 (30.4)*	1.80 [1.41; 2.28]; < 0.001
Arthralgia (PT, AE)	344	n.a. *57 (16.6)*	345	n.a. *20 (5.8)*	2.59 [1.55; 4.32]; < 0.001

Respiratory, thoracic and mediastinal disorders (SOC, AE)	344	20.2 [14.8; n. c.] *101 (29.4)*	345	n.a. *36 (10.4)*	2.53 [1.72; 3.70]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AE)	344	15.1 [9.6; 24.1] *144 (41.9)*	345	n.a. *28 (8.1)*	5.94 [3.96; 8.91]; < 0.001
Lipase elevated (PT, severe AE)	344	n.a. *14 (4.1)*	345	n.a. *1 (0.3)*	12.83 [1.68; 97.85]; 0.002
Amylase elevated (PT, severe AE)	344	n.a. *12 (3.5)*	345	n.a. *2 (0.6)*	5.28 [1.17; 23.73]; 0.015
Metabolism and nutrition disorders (SOC, severe AE)	344	n.a. *29 (8.4)*	345	n.a. *11 (3.2)*	2.24 [1.11; 4.50]; 0.021
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC, severe AE)	344	n.a. *9 (2.6)*	345	n. a. [26.0; n. c.] *17 (4.9)*	0.40 [0.18; 0.91]; 0.023

[a] Absolute difference (AD) is given only in the case of a statistically significant difference; own calculation
[b] Information from the dossier (module 4) of the pharmaceutical company

Abbreviations used:
AD = absolute difference; BSC = best supportive care; CTCAE = Common Terminology Criteria for Adverse Events; DRS-P: Disease related Symptoms-Physical; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; HR = hazard ratio; CI = confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n. c. = not calculable; n. a. = not achieved; NFBISI-18 = NCCN/FACT Bladder Symptom Index-18; PT: preferred term; RCT: randomized controlled trial, SOC: System organ class; SAE: serious adverse event; TSE: treatment side effects; AE: adverse event; VAS: visual analogue scale; vs = versus

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

Adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy; first-line maintenance treatment:

approx. 4,125 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 Bavencio (active ingredient: avelumab) at the following publicly accessible link (last access: 27 May 2021):

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

Treatment with avelumab should only be initiated and monitored by specialists in internal medicine, haematology, oncology, urology and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with urothelial carcinoma.

In accordance with EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient card. Patients are requested to carry the patient card with them at all times. The training material for health professionals and the patient card contain, in particular, instructions on how to deal with the immune-mediated side effects that can potentially occur with avelumab.

4. Treatment costs

Annual treatment costs:

Adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy; first-line maintenance treatment:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Avelumab	€ 82,182.64
Best supportive care	Patient-individual
Appropriate comparator therapy:	
Best supportive care	Patient-individual

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 August 2021)

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Avelumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 19 August 2021.

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

Berlin, 19 August 2021

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

Prof. Hecken