Resolution

Gemeinsamer Bundesausschuss

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: Renal Cell Carcinoma, First-Line, Combination with Axitinib)

of 14 May 2020

At its session on 14 May 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. 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 16 March 2018:

Avelumab

Resolution of: 14 May 2020
Entry into force on: 14 May 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 24 October 2019):

Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) (see section 5.1).

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

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

Appropriate comparator therapy:

- Bevacizumab in combination with interferon alfa-2a

  or
- Nivolumab in combination with ipilimumab (only for patients with intermediate risk profile)

  or
- Monotherapy with pazopanib

  or
- Monotherapy with sunitinib

Extent and probability of the additional benefit of avelumab in combination with axitinib compared with sunitinib:

An additional benefit is not proven

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

Appropriate comparator therapy:

- Nivolumab in combination with ipilimumab

  or
- Sunitinib

  or
- Temsirolimus

Extent and probability of the additional benefit of avelumab in combination with axitinib compared with sunitinib:

Hint for a considerable additional benefit

Study results according to endpoints[1]:

Study: Javelin Renal 101; avelumab + axitinib vs sunitinib

Study design: randomised, open-label, Phase III

Data cut-off: 28 January 2019

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

Mortality

Endpoint	**Avelumab + axitinib**		**Sunitinib**		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 (%)*	Hazard Ratio [95% CI] p value[a] Absolute difference (AD)[b]
Overall survival					
	365	n.a. [30.0; n.a.] *74 (20.3)*	372	n.a. [28.6; n.a.] *84 (22.6)*	0.87 [0.63; 1.19] 0.378

Morbidity

Progression-free survival (PFS)[c]					
	365	n.a. [n.a.; n.a.] *97 (26.6)*	372	23.8 [18.6; 28.6] *142 (38.2)*	0.57 [0.44; 0.74] < 0.0001 AD: n.c.

Endpoint	**Avelumab + axitinib**			**Sunitinib**			Intervention vs control
	N	Values at start of study MV (SD)	Change MV[d] [95% CI]	N	Values at start of study MV (SD)	Change MV[d] [95% CI]	MD [95% CI][e] p value
Symptomatology							
FKSI-DRS	334	no data available	- 1.33 [−1.65; −1.01]	342	no data available	- 1.22 [−1.55; −0.88]	- 0.11 [−0.57; 0.35] 0.643

(Continuation)

[1] Data from the dossier assessment of the IQWiG (A19-95) and from the addendum (A20-41) unless otherwise indicated.

Health status							
EQ-5D VAS	336	no data availabl e	- 1.17 [−2.39; 0.04]	343	no data availabl e	- 1.53 [−2.80; −0.27]	0.36 [−1.40; 2.11] 0.689

Health-related quality of life

Endpoint not surveyed

Side effects

Endpoint	**Avelumab + axitinib**		**Sunitinib**		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 (%)*	Hazard Ratio [95% CI] p value[a] Absolute difference (AD)[b]
Total adverse events (presented additionally)[f]					
	358	0.1 [0.1; 0.1] *357 (99.7)*	368	0.3 [0.2; 0.3] *366 (99.5)*	-
Serious adverse events (SAE)[f]					
	358	25.0 [19.2; n.a.] *136 (38.0)*	368	26.3 [22.8; n.a.] *107 (29.1)*	1.09 [0.85; 1.41] 0.496
Severe adverse events (CTCAE grade ≥ 3)[f]					
	358	2.8 [2.3; 4.2] *273 (76.3)*	368	2.3 [1.8; 3.3] *281 (76.4)*	0.85 [0.72; 1.01] 0.057
Therapy discontinuation because of adverse events[g]					
	358	n.a. *86 (24.0)*	368	n.a. *49 (13.3)*	1.69 [1.19; 2.40] 0.003 AD: n.c.
Specific adverse events					
Immune mediated AE	No usable data				

(Continuation)

Infusion-related reactions	No usable data				
Diarrhoea (PT, severe AE [CTCAE grade ≥ 3])	358	n.a. *35 (9.8)*	368	n.a. *10 (2.7)*	2.80 [1.39; 5.66] 0.003 AD: n.c.
Dyspepsia (PT, AE)	358	n.a. *33 (9.2)*	368	n.a. *79 (21.5)*	0.34 [0.23; 0.51] < 0.001 AD: n.c.
Chills (PT, AE)	358	n.a. *63 (17.6)*	368	n.a. *33 (9.0)*	2.00 [1.30; 3.06] 0.001 AD: n.c.
Pruritus (PT, AE)	358	n.a. *65 (18.2)*	368	n.a. *23 (6.3)*	2.64 [1.64; 4.25] < 0.001 AD: n.c.
Increased alanine transaminase increased (PT, severe AE [CTCAE grade ≥ 3])	358	n.a. *25 (7.0)*	368	n.a. *9 (2.4)*	2.57 [1.20; 5.51] 0.012 AD: n.c.
Dysphonia (PT, AE)	358	n.a. *132 (36.9)*	368	n.a. *16 (4.3)*	10.05 [5.98; 16.90] < 0.001 AD: n.c.
Taste disorder (PT, AE)	358	n.a. *53 (14.8)*	368	n.a. [21.3; n.a.] *133 (36.1)*	0.31 [0.23; 0.43] < 0.001 AD: n.c.
Blood and lymphatic system disorders (SOC, severe AE [CTCAE grade ≥ 3])	358	n.a. *8 (2.2)*	368	n.a. *73 (19.8)*	0.09 [0.04; 0.18] < 0.001 AD: n.c.

[a] Effect and confidence interval (CI): Cox Proportional Hazards Model, p value: Log rank test; for overall survival and EQ-5D VAS: stratified by ECOG-PS (0 vs 1) and region (US vs Canada and Western Europe vs rest of the world)
[b] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation.

(Continuation)

[c] Information from the dossier of the pharmaceutical company
[d] Least squares mean [95% CI]; positive values represent an improvement; positive effects mean an advantage for intervention.
[e] MMRM; stratification factors of randomisation are not included in the model. No information is available on whether the changes per treatment group and the MD refer to the changes averaged over the entire course of the study compared with the start of study or to changes compared with the start of study.
[f] Without recording of events based on progression of the underlying disease
[g] In the intervention arm, the data refer to the discontinuation of at least 1 active ingredient (avelumab or axitinib).

Abbreviations used:
AD: Absolute difference; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease related Symptoms; CI: confidence interval; MD: mean difference; MMRM: Mixed Model for repeated Measurements; MV: mean value; n: number of patients with (at least one) event; N: number of patients evaluated; n.c.: not calculable; n.a.: not achieved; PT: preferred term; SD: standard deviation; SOC: system organ class; AE: adverse event; VAS: visual analogue scale; vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment.
Morbidity	↔	No differences relevant for the benefit assessment.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	↓	Disadvantage in the endpoint discontinuation of therapy because of AE; advantage and disadvantage in individual 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

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

Mortality

Endpoint	**Avelumab + axitinib**		**Sunitinib**		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 (%)*	Hazard Ratio [95% CI] p value[a] Absolute difference (AD)[b]
Overall survival					
	72	21.2 [14.7; 26.3] *33 (45.8)*	71	11.0 [7.8; 16.5] *45 (63.4)*	0.50 [0.31; 0.81] 0.005 AD: 10.2 months
Effect modification by the characteristic region					
North America	16	17.7 [6.4; n.a.] *10 (62.5)*	20	18.9 [5.8; 25.5] *12 (60.0)*	0.90 [0.39; 2.10] 0.811
Europe	31	16.0 [9.1; n.a.] *14 (45.2)*	40	11.6 [8.0; 16.9] *24 (60.0)*	0.69 [0.36; 1.34] 0.272
Asia	14	23.8 [9.6; n.a.] *5 (35.7)*	4	11.5 [2.8; n.a.] *3 (75.0)*	0.45 [0.10; 1.91] 0.265
Rest of the world	11	19.9 [2.8; n.a.] *4 (36.4)*	7	4.2 [0.8; 13.5] *6 (85.7)*	0.15 [0.04; 0.65] 0.005 AD: 15.7 months
				Interaction:	p = 0.045[h]

Morbidity

Progression-free survival (PFS)[c]					
	72	19.9 [10.7; n.a.] *43 (47.2)*	71	7.4 [6.0; 10.4] *50 (70.4)*	0.43 [0.27; 0.69] 0.0004 AD: 12.4 months

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Endpoint	Avelumab + axitinib			Sunitinib			Intervention vs control
	N	Values at start of study MV (SD)	Change MV[d,e] [95% CI]	N	Values at start of study MV (SD)	Change MV[d,e] [95% CI]	MD [95% CI][e] p value
Symptomatology							
FKSI-DRS	65	no data available	1.36 [0.09; 2.64]	59	no data available	- 0.71 [−2.29; 0.87]	2.07 [0.04; 4.10] 0.045 SMD: 0.37 [0.01; 0.72] 0.043
Health status							
EQ-5D VAS	65	no data available	4.66 [0.48; 8.85]	57	no data available	- 5.27 [−10.3; −0.19]	9.93 [3.36; 16.50] 0.036 SMD: 0.55 [0.19; 0.91] 0.003

Health-related quality of life

Endpoint not surveyed

Side effects

Endpoint	Avelumab + axitinib		Sunitinib		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 (%)*	Hazard Ratio [95% CI] p value[a] Absolute difference (AD)[b]
Total adverse events (presented additionally)[f]					
	72	0.1 [0.0; 0.2] *72 (100.0)*	70	0.2 [0.2; 0.4] *69 (98.6)*	-

(Continuation)

Serious adverse events (SAE)[f]					
	72	9.8 [3.5; n.a.] *38 (52.8)*	70	6.5 [3.8; n.a.] *31 (44.3)*	0.94 [0.58; 1.52] 0.787
Severe adverse events (CTCAE grade ≥ 3)[f]					
	72	1.9 [1.4; 3.1] *59 (81.9)*	70	2.2 [1.4; 4.1] *48 (68.6)*	1.08 [0.73; 1.59] 0.699
Therapy discontinuation because of adverse events[g]					
	72	16.9 [9.0; n.a.] *29 (40.3)*	70	n.a. [10.3; n.a.] *13 (18.6)*	1.81 [0.93; 3.51] 0.075 AD: n.c.
Specific adverse events					
Immune mediated AE	No usable data				
Infusion-related reactions	No usable data				
Gastrointestinal disorders (SOC severe AE [CTCAE grade ≥ 3])	72	n.a. *7 (9.7)*	70	n.a. *14 (20.0)*	0.32 [0.13; 0.81] 0.012 AD: n.c.
Hypertension (PT, severe AE [CTCAE grade ≥ 3])	72	n.a. *21 (29.2)*	70	n.a. *7 (10.0)*	2.92 [1.24; 6.90] 0.011 AD: n.c.
Blood and lymphatic system disorders (SOC, severe AE [CTCAE grade ≥ 3])	72	n.a. *5 (6.9)*	70	7.1 [5.6; n.a.] *25 (35.7)*	0.11 [0.04; 0.28] < 0.001 AD: n.c.
Hypothyroidism[h] (PT, AE)	72	n.a. [9.7; n.a.] *21 (29.2)*	70	n.a. *4 (5.7)*	4.49 [1.54; 13.13] 0.003 AD: n.c.

[a] Effect and confidence interval (CI): Cox Proportional Hazards Model, p value: Log rank test; for overall survival: stratified by ECOG-PS (0 vs 1) and region (US vs Canada and Western

(Continuation)

Europe vs rest of the world)

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

[c] Information from the dossier of the pharmaceutical company

[d] Least squares mean; positive values represent an improvement; positive effects mean an advantage for intervention.

[e] MMRM; stratification factors of randomisation are not included in the model. No information is available on whether the changes per treatment group and the MD refer to the changes averaged over the entire course of the study compared with the start of study or to changes at only one time compared with the start of study.

[f] Without recording of events based on progression of the underlying disease

[g] In the intervention arm, the data refer to the discontinuation of at least 1 active ingredient (avelumab or axitinib).

[h] Most of these patients (15 [20.8%] in the avelumab + axitinib arm and 3 [4.3%] in the sunitinib arm) had a CTCAE grade 2 event associated with symptomatology.

Abbreviations used:

AD: Absolute difference; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease related Symptoms; CI: confidence interval; MD: mean difference; MMRM: Mixed Model for repeated Measurements; MV: mean value; n: number of patients with (at least one) event; N: number of patients evaluated; n.c.: not calculable; n.a.: not achieved; PT: preferred term; SD: standard deviation; SMD: standardised mean difference, similar to Hedges' g; SOC: system organ class; AE: adverse event; VAS: visual analogue scale; vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	↔	No differences relevant for the benefit assessment.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
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

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

approx. 2,700 patients

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

approx. 800 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: 5 May 2020):

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

Treatment with avelumab may only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and nephrology, and other specialists participating in the Oncology Agreement who are experienced in the treatment of patients with renal cell carcinoma.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on avelumab:

- Training and information material for medical professionals
- Training and information material for the patient

The Javelin Renal 101 study exclusively investigated patients with renal cell carcinoma with clear cell histology. No data are available for patients with non-clear-cell renal cell carcinoma.

This medicinal product was approved under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. 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:

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Avelumab in combination with axitinib	
Avelumab	€ 99,052.63
Axitinib	€ 46,868.22
Total	€ 145,920.85
Appropriate comparator therapy:	
Bevacizumab in combination with interferon alfa-2a	
Bevacizumab	€ 83,251.69
Interferon alfa-2a	€ 15,508.68
Total	€ 98,760.37
Nivolumab in combination with ipilimumab	
Initial treatment	
Nivolumab	€ 12,201.36
Ipilimumab	€ 29,046.08
Total	€ 41,247.44
Follow-up treatment	
Nivolumab	€ 56,736.32 – 61,311.83
Initial treatment + total follow-up treatment	€ 102,559.27 – 97,983.76
Monotherapies	
Pazopanib	€ 54,403.13
Sunitinib	€ 55,245.07

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2020

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Avelumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Appropriate comparator therapy:					
Bevacizumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Nivolumab in combination with ipilimumab					
Nivolumab (follow-up treatment with nivolumab in 14-day cycle)	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	24.1	€ 1,711.10
Nivolumab (follow-up treatment with nivolumab in 28-day cycle)	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	13.3	€ 944.30
Ipilimumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	4	€ 284.00
Total					€ 1,228.30 – 1,995.10

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Avelumab in combination with axitinib	
Avelumab	€ 99,052.63
Axitinib	€ 46,868.22
Total	€ 145,920.85
Appropriate comparator therapy:	
Nivolumab in combination with ipilimumab	
Initial treatment	
Nivolumab	€ 12,201.36
Ipilimumab	€ 29,046.08
Total	€ 41,247.44
Follow-up treatment	Follow-up treatment
Nivolumab	€ 56,736.32 – 61,311.83
Initial treatment + total follow-up treatment	€ 102,559.27 – 97,983.76
Monotherapies	
Sunitinib	€ 55,245.07
Temsirolimus	€ 58,154.54

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2020

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Avelumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	26.1	€ 1,853.10

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Appropriate comparator therapy:					
Nivolumab in combination with ipilimumab					
Nivolumab (follow-up treatment with nivolumab in 14-day cycle)	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	24.1	€ 1,711.10
Nivolumab (follow-up treatment with nivolumab in 28-day cycle)	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	13.3	€ 944.30
Ipilimumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	4	€ 284.00
Total					€ 1,228.30 – 1,995.10
Temsirolimus	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	52.1	€ 4,220.10

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 14 May 2020.

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

Berlin, 14 May 2020

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

Prof. Hecken