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 Pembrolizumab (New Therapeutic Indication: Head And Neck Squamous Cell Carcinoma, First Line, Monotherapy)

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 pembrolizumab in accordance with the resolutions of 19 September 2019, last amended on 28 January 2020 (Federal Gazette, BAnz AT 2 March 2020 B2):

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Pembrolizumab

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 14 November 2019):

KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Note:

This assessment relates exclusively to the assessment of the additional benefit of pembrolizumab as monotherapy. For the assessment of the additional benefit of pembrolizumab in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, reference is made to the separate benefit assessment procedure for this combination therapy.

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

Adult patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 (combined positive score [CPS] ≥ 1); first-line treatment

Appropriate comparator therapy:

- Cetuximab + cisplatin or carboplatin + 5-FU

Exclusively to the assessment of the additional benefit of pembrolizumab as monotherapy compared with cetuximab in combination with platinum and 5-fluorouracil (5-FU) chemotherapy:

Hint for a considerable additional benefit.

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Study results according to endpoints:[1]

Adult patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 (combined positive score [CPS] ≥ 1); first-line treatment

KEYNOTE 048 study: **Pembrolizumab vs** pembrolizumab + cisplatin/carboplatin + 5-FU vs **cetuximab + cisplatin/carboplatin + 5-FU**

Relevant sub-population: Patients whose tumours express PD-L1 (combined positive score [CPS] ≥ 1)

Mortality

Endpoint	**Pembrolizumab**		**Cetuximab + cisplatin/ carboplatin + 5-FU**		**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 Absolute difference (AD)[a]
Overall survival					
	257	12.3 [10.8; 14.3] 197 (76.7)	255	10.3 [9.0; 11.5] 229 (89.8)	0.74 [0.61; 0.90] 0.003 AD = 2.0 months
Sub-groups according to illness status					
metastatic	179	13.1 [10.8; 16.8] 132 (73.7)	168	9.7 [8.5; 11.2] 153 (91.1)	0.62 [0.49; 0.79] < 0.001 AD = 3.4 months
recurrent	75	11.5 [7.8; 13.0] 64 (85.3)	84	12.1 [9.2; 13.9] 74 (88.1)	1.04 [0.74; 1.45] 0.835
Total					Interaction: 0.016

[1] Data from the dossier assessment of the IQWiG (A19-100) unless otherwise indicated.

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Morbidity

Endpoint	Pembrolizumab		Cetuximab + cisplatin/ carboplatin + 5-FU		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 Absolute difference (AD)[a]
Progression-free survival (PFS)[2]					
	257	3.2 [2.2; 3.4] 228 (88.7)	255	5.0 [4.8; 6.0] 237 (92.9)	1.13 [0.94; 1.36] 0.202
Symptomatology (EORTC QLQ-C30 symptom scales)					
No usable data					
Symptomatology (EORTC QLQ-H&N35 symptom scales)					
No usable data					
Health status (EQ-5D VAS)					
No usable data					

Endpoint	Pembrolizumab		Cetuximab + cisplatin/ carboplatin + 5-FU		Intervention vs control
	N	Values at start of study MV (SD) Value at Week 9 MV (SD)	N	Values at start of study MV (SD) Value at Week 9 MV (SD)	Mean difference [95% CI] p value
Health status (EQ-5D VAS) (presented as a supplement)					
	192	68 (18.5) 72.5 (18.4)	185	66.5 (19.9) 72 (16.8)	0.50 [−3.07; 4.07] 0.783

[2] Data from the dossier on pembrolizumab monotherapy (Module 4A) submitted on 29 November 2019

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Health-related quality of life

Endpoint	Pembrolizumab		Cetuximab + cisplatin/ carboplatin + 5-FU		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 Absolute difference (AD)[a]
EORTC QLQ-C30 functional scales					
No usable data					
EORTC QLQ-H&N35 functional scales					
No usable data					

Side effects

Endpoint	Pembrolizumab		Cetuximab + cisplatin/ carboplatin + 5-FU		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 Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	256	0.5 [0.3; 0.6] 248 (96.9)	245	0.4 [0.1; 0.1] 244 (99.6)	-
Serious adverse events (SAE)					
	256	21.4 [9.7; n.c.] 106 (41.4)	245	10.6 [5.2; n.c.] 121 (49.4)	0.78 [0.60; 1.02] 0.067
Severe adverse events (CTCAE grade ≥ 3)					
	256	5.5 [3.2; 9.0] 140 (54.7)	245	0.9 [0.7; 1.2] 203 (82.9)	0.41 [0.33; 0.51] < 0.001 AD = 4.6 months
Therapy discontinuation because of adverse events					
	256	n.a. 30 (11.7)	245	39.3 [39.3; n.c.] 67 (27.3)	0.39 [0.25; 0.60] < 0.001
Specific adverse events [b]					
Immune-mediated AEs (additionally	256	10.4 [9.0; 21.4]	245	n.a.	-

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Endpoint	Pembrolizumab		Cetuximab + cisplatin/ carboplatin + 5-FU		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 Absolute difference (AD)[a]
shown)		81 (31.6)		59 (24.1)	
Immune-mediated SAE	256	n.a. 18 (7.0)	245	n.a. 10 (4.1)	1.66 [0.76; 3.61] 0.204
Immune-mediated severe AEs (CTCAE grade ≥ 3)	256	n.a. 21 (8.2)	245	n.a. 27 (11.0)	0.65 [0.36; 1.16] 0.142
Paronychia (PT, AEs)	256	no data available 1 (0.4)	245	no data available 30 (12.2)	RR: 0.03 [0.0; 0.23] < 0.001
Skin and subcutaneous tissue disorders (SOC severe AEs [CTCAE grade ≥ 3])	256	n.a. 10 (3.9)	245	n.a. 24 (9.8)	0.37 [0.17; 0.77] 0.008
Ear and labyrinth disorders (SOC, AEs)	256	n.a. 21 (8.2)	245	n.a. [33.3; n.c.] 44 (18.0)	0.44 [0.26; 0.75] 0.002
Asthenia (PT, AEs)	256	no data available 13 (5.1)	245	no data available 32 (13.1)	RR: 0.39 [0.21; 0.72] 0.002
Dizziness (PT, AEs)	256	no data available 12 (4.7)	245	no data available 29 (11.8)	RR: 0.40 [0.21; 0.76] 0.004
Blood and lymphatic system disorders (SOC severe AEs [CTCAE grade ≥ 3])	256	n.a. 15 (5.9)	245	n.a. 90 (36.7)	0.13 [0.08; 0.23] < 0.001
Anaemia (PT, AEs ([CTCAE grade ≥ 3])	256	no data available 12 (4.7)	245	no data available 36 (14.7)	RR: 0.32 [0.17; 0.60] < 0.001
Gastrointestinal disorders (SOC AEs [CTCAE grade ≥ 3])	256	n.a. 18 (7.0)	245	n.a. 42 (17.1)	0.38 [0.22; 0.67] < 0.001
Mucosa inflammation (PT, AEs [CTCAE grade ≥ 3])	256	no data available 4 (1.6)	245	no data available 13 (5.3)	RR: 0.29 [0.10; 0.89] 0.022
Investigations (SOC, AEs [CTCAE grade	256	n.a.	245	n.a.	0.42 [0.26; 0.67]

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Endpoint	Pembrolizumab		Cetuximab + cisplatin/ carboplatin + 5-FU		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 Absolute difference (AD)[a]
≥ 3]) [c]		26 (10.2)		55 (22.4)	< 0.001
Hypomagnesaemia (PT, AEs [CTCAE grade ≥ 3])	256	no data available 0 (0)	245	no data available 10 (4.1)	RR: 0.05 [0.00; 0.77] 0.001
Respiratory, thoracic, and mediastinal disorders (SOC, AEs [CTCAE grade ≥ 3])	256	n.a. 33 (12.9)	245	n.a. 18 (7.3)	1.82 [1.02; 3.24] 0.042

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Selection in accordance with IQWiG methodology; selection based on those identified in the study Events based on frequency and differences between treatment arms and taking into account patient relevance.
[c] This includes the following PTs with statistically significant differences between treatment groups: "Reduced neutrophil number" and "reduced leukocyte number".

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	n.a.	No data suitable for the benefit assessment.
Side effects	↑	Advantages in the endpoints severe AE (CTCAE grade ≥ 3), therapy discontinuation because of AE; primarily advantages 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

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n.a.: not assessable

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

approx. 4,950–5,370 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 Keytruda® (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 8 April 2020):

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

Treatment with pembrolizumab may only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in otorhinolaryngology, and other specialists participating in the Oncology Agreement who are experienced in the treatment of patients with head and neck tumours. 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 pembrolizumab:

− Training and information material for doctors/medical professionals

− Training and information material for the patient

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pembrolizumab	€ 101,243.99
Appropriate comparator therapy:	
Cisplatin + 5-fluorouracil + cetuximab	
Cisplatin	€ 2,486.11
+ 5-fluorouracil	€ 928.19
+ cetuximab	€ 73,218.36
Total:	€ 76,632.66
Additionally required SHI service	€ 328.58 – 421.62
Carboplatin + 5-fluorouracil + cetuximab	
Carboplatin	€ 6,858.73
+ 5-fluorouracil	€ 928.19

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Designation of the therapy	Annual treatment costs/patient
+ cetuximab	€ 73,218.36
Total:	€ 81,005.28

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

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					
Pembrolizumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	8.7	€ 617.70
				17.4	€ 1,235.40
Appropriate comparator therapy					
Cisplatin + 5-fluorouracil + cetuximab or carboplatin + 5-fluorouracil + cetuximab					
Cisplatin or Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4	69.6	€ 5637.60
Cetuximab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	52.1	€ 3,699.10

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.

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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

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