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
Cemiplimab (new therapeutic indication: basal cell carcinoma, locally advanced or metastatic)

of 20 January 2022

At its session on 20 January 2022, 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 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. 4 to the information on the benefit assessment of Cemiplimab in accordance with the resolution of 20 January 2022:

Cemiplimab

Resolution of: 20 January 2022
Entry into force on: 20 January 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

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

LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).

Therapeutic indication of the resolution (resolution of 20 January 2022):

see new therapeutic indication according to marketing authorisation

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

Adults with locally advanced or metastatic basal cell carcinoma (BCC) who have been previously treated with a Hedgehog pathway inhibitor and show disease progression or intolerance to it during this treatment.

Appropriate comparator therapy:

- Best supportive care

Extent and probability of the additional benefit of Cemiplimab compared to the appropriate comparator therapy:

a) Adults with locally advanced basal cell carcinoma (laBCC) who have been previously treated with a Hedgehog pathway inhibitor and show disease progression or intolerance to it during this treatment.

Hint for a minor additional benefit

b) Adults with metastatic basal cell carcinoma (mBCC) who have been previously treated with a Hedgehog pathway inhibitor and show disease progression or intolerance to it during this treatment.

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults with locally advanced basal cell carcinoma (laBCC) who have been previously treated with a Hedgehog pathway inhibitor and show disease progression or intolerance to it during this treatment.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	↑	Clinical response advantage
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
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) Adults with metastatic basal cell carcinoma (mBCC) who have been previously treated with a Hedgehog pathway inhibitor and show disease progression or intolerance to it during this treatment.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
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		

[1] Data from the dossier assessment of the IQWiG (A21-97) and from the addendum (A21-161), unless otherwise indicated.

∅: There are no usable data for the benefit assessment.
n.a.: not assessable

R2810-ONC-1620 study: single-arm, open-label and multicentre phase II study

Data cut-off: 1. Data cut-off of 17 February 2020

Mortality

Endpoint	**Cemiplimab**	
	laBCC+ mBCC	
	N	Median survival time in months [95% CI] *Patients with event n (%)*
Overall survival[a] (presented additionally)		
	112	25.7 [25.7; n.c.] *17 (15.2)*

Morbidity

Endpoint	**Cemiplimab**			
	laBCC		**mBCC**	
	N	*Patients with event n (%)* [95% CI]	N	*Patients with event n (%)* [95% CI]
Objective response rate (ORR)[a] (presented additionally)				
	84	*24 (28.6)* [19.2; 39.5]	28	*6 (21.4)* [8.30; 40.95]

Endpoint	**Cemiplimab**	
	laBCC	
	N	*Patients with clinical response (%)*
Overall clinical response[b]		
Number of patients	81[c]	24 (30)

Number of lesions (N_L)	109[c]	31
Clinical response according to lesion size[b]		
Category 1 (> 50 mm)		
Number of patients	31[d]	7 (23)
Number of lesions (N_L)	47[d]	12
Category 2 (≤ 50 mm)		
Number of patients	39[e]	17 (44)
Number of lesions (N_L)	51[e]	19

Type of clinical response (operationalisation according to ERIVANCE)	Type of clinical response (operationalisation according to R2810-ONC-1620)	Lesion size over the course (MV)
Characterisation of clinical response according to lesion size[b]		
Category 1 (N = 7; N_L = 12; minimum lesion size: 54.4 mm[f]; maximum lesion size: 96.97 mm)		
Phase 1: complete remission of the lesion(s) by 100% and elimination of the ulceration(s)	CR: n = 1 PR: n = 6	Patient level[g]: *Start of study: 96.4 mm* *In the case of response: 58.7 mm* *Reduction: 39.1%* Lesion level: *Start of study: 56.3 mm* *In the case of response: 34.3 mm* *Reduction: 39.1%*
n = 1		
Phase 2: significant, incomplete reduction of the lesion(s) by at least 30% and < 100% and elimination of the ulceration(s)		
n = 5		
Phase 3: significant, incomplete reduction of the lesion(s), but persistent ulceration(s) *or* no/low reduction of lesion(s) by < 30%, but elimination of ulceration(s)		
n = 1		

Category 2 (N = 17; N_L = 19; minimum lesion size: 8.56 mm; maximum lesion size: 46.39 mm)		
Phase 1: complete remission of the lesion(s) by 100% and elimination of the ulceration(s)	CR: n = 8 PR: n = 9	Patient level[g]: *Start of study: 30.5 mm* *In the case of response: 10.7 mm* *Reduction: 64.8%* Lesion level: *Start of study: 27.3 mm* *In the case of response: 9.6 mm* *Reduction: 64.8%*
n = 8		
Phase 2: significant, incomplete reduction of the lesion(s) by at least 30% and < 100% and elimination of the ulceration(s)		
n = 7		
Phase 3: significant, incomplete reduction of the lesion(s), but persistent ulceration(s) *or* no/low reduction of lesion(s) by < 30%, but elimination of ulceration(s)		
n = 2		

Endpoint	**Cemiplimab**	
	laBCC + mBCC	
	N	Median time to event in months [95% CI] *Patients with event n (%)*
Progression-free survival (PFS)[a] (presented additionally)		
	112	13.1 [8.3; 21.3] *55 (49.1)*
Symptomatology (EORTC QLQ-C30)		
	There are no assessable data.	

Health-related quality of life

There are no assessable data.

Side effects

Endpoint	Cemiplimab	
	laBCC + mBCC	
	N	*Patients with event n (%)* [95% CI]
Total adverse events[a] (presented additionally)		
	132	*125 (94.7)* [89.4; 97.8]
Serious adverse events (SAE)[a] (presented additionally)		
	132	*42 (31.8)* [24.0; 40.5]
Severe adverse events (CTCAE grade 3 or 4)[a] (presented additionally)		
	132	*59 (44.7)* [36.0; 53.6]
Therapy discontinuations due to adverse events[a] (presented additionally)		
	132	*17 (12.9)* [7.7; 19.8]
Adverse Events of special interest[a] (presented additionally)		
Immune reactions ≥ grade 3	132	*15 (11.4)* [6.5; 18.0]
Infusion-related reactions ≥ grade 2	132	*4 (3.0)* [0.8; 7.6]
Allergic reactions ≥ grade 2	132	*1 (0.8)* [0.0; 4.1]
Immune reactions of any grade after pre-treatment with a PI3K inhibitor	132	0

[a] Data from module 4 of the pharmaceutical company from 16.07.2021
[b] Data from IQWiG's addendum of 21.12.2021
[c] Information for 3 patients missing; clinical response cannot be evaluated for 20 lesions in 17 patients.
[d] Category cannot be determined for 11 patients with 1 lesion each. Clinical response cannot be evaluated for 3 lesions in 3 patients.
[e] Category cannot be determined for 11 patients with 1 lesion each. Clinical response cannot be evaluated for 6 lesions in 3 patients.
[f] For category 1, specified minimum lesion size of lesions > 50 mm, individual patients with additional target lesions < 50 mm; the smallest target lesion for patients in category 1 was 22.24 mm.
[g] Mean value of the summed lesion sizes (sum of the target lesions per patient)

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; ICR = independent central review; 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; PT = preferred term; SOC = system organ class; vs = versus

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

a) Adults with locally advanced basal cell carcinoma (laBCC) who have been previously treated with a Hedgehog pathway inhibitor and show disease progression or intolerance to it during this treatment.

approx. 80 – 150 patients

b) Adults with metastatic basal cell carcinoma (mBCC) who have been previously treated with a Hedgehog pathway inhibitor and show disease progression or intolerance to it during this treatment.

approx. 3 – 5 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 Libtayo (active ingredient: cemiplimab) at the following publicly accessible link (last access: 28 September 2021):

https://www.ema.europa.eu/en/documents/product-information/libtayo-epar-product-information_en.pdf

Treatment with cemiplimab should only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of adults with basal cell carcinoma, specialists in skin and sexually transmitted diseases as well as other doctors from specialist groups participating in the Oncology Agreement.

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 cemiplimab:

- information brochure for patients
- patient pass

The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with cemiplimab as well as on infusion-related reactions.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines

Agency 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) Adults with locally advanced basal cell carcinoma (laBCC) who have been previously treated with a Hedgehog pathway inhibitor and show disease progression or intolerance to it during this treatment.

and

b) Adults with metastatic basal cell carcinoma (mBCC) who have been previously treated with a Hedgehog pathway inhibitor and show disease progression or intolerance to it during this treatment.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Cemiplimab	€ 74,660.27
Best supportive care	Different from patient to patient
Appropriate comparator therapy:	
Best supportive care	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®as last revised: 1 January 2022)

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Cemiplimab	Surcharge for the production of a parenteral solution with monoclonal antibodies	€ 71	1	17.4	€ 1,235.40

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 January 2022.

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

Berlin, 20 January 2022

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

Prof. Hecken