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: Lenvatinib (Reassessment after the deadline: Advanced renal cell carcinoma, combination with Everolimus)

of 1 July 2021

At its session on 1 July 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. Annex XII is amended as follows:

1. The information on lenvatinib in the version of the resolution of 16 March 2017 (BAnz AT 21.04.2017 B1) is repealed.

2. Annex XII shall be amended in alphabetical order to include the active ingredient lenvatinib as follows:

Lenvatinib

Resolution of: 1 July 2021
Entry into force on: 1 July 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 25 August 2016):

Kisplyx is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Therapeutic indication of the resolution (resolution of 1 July 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 advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy

   Appropriate comparator therapy:

   Nivolumab or cabozantinib

   Extent and probability of the additional benefit of lenvatinib in combination with everolimus compared to cabozantinib:

   An additional benefit is not proven

Study results according to endpoints[1]:

Adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	n.a.	There are no usable data for the benefit assessment
Health-related quality of life	∅	No data available
Side effects	↔	No relevant difference 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

Adjusted indirect comparison

Lenvatinib + everolimus versus cabozantinib via the bridging comparator everolimus

205 study: Lenvatinib + everolimus **vs** everolimus; open-label phase 1b/2 study

METEOR study: Cabozantinib vs everolimus; open-label phase 3 study

1 Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A20-122) unless otherwise indicated.

Mortality

Endpoint	Lenvatinib + everolimus or cabozantinib		Everolimus (bridge comparator)		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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Mortality					
Lenvatinib + everolimus vs everolimus (data cut-off from 31.7.2015)					
	51	25.5 [16.4; 32.1] 32 (62.7)	50	15.4 [11.8; 20.6] 37 (74.0)	0.59 [0.36; 0.97]; 0.036
Cabozantinib vs everolimus (data cut-off from 2.10.2016)					
	330	21.4 [18.6; 23.5] 198 (60.0)	328	17.1 [14.9; 18.9] 232 (70.7)	0.70 [0.58; 0.85]; < 0.001
Adjusted indirect compare[b]: Lenvatinib + everolimus vs cabozantinib					0.84 [0.50; 1.43]; n. d.

Morbidity

Endpoint	Lenvatinib + everolimus or cabozantinib		Everolimus (bridge comparator)		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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Progression-free survival[c]					
Lenvatinib + everolimus vs everolimus (data cut-off from 13.6.2014)					
	51	12.8 [7.4; 17.5] 24 (47.1)	50	5.6 [3.6; 9.3] 29 (58.0)	0.45 [0.26; 0.79]
Cabozantinib vs everolimus (data cut-off from 2.10.2016)					
	330	n. d. 180 (55)	328	n. d. 214 (65)	0.52 [0.43; 0.64]
Adjusted indirect compare[b]: Lenvatinib + everolimus vs cabozantinib					0.87 [0.48; 1.56] n. d.

(continuation)

Endpoint	Lenvatinib + everolimus or cabozantinib		Everolimus (bridge comparator)		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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Symptomatology (FKSI-DRS)	only collected in the METEOR study				
Health status (EQ-5D VAS)	only collected in the METEOR study				
skeletal associated events	only collected in the METEOR study				

Health-related quality of life

Endpoint	Lenvatinib + everolimus or cabozantinib		Everolimus (bridge comparator)		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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
No data on health-related quality of life were assessed in both studies.					

Side effects

Endpoint	Lenvatinib + everolimus or cabozantinib		Everolimus (bridge comparator)		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
Lenvatinib + everolimus vs everolimus (data cut-off from 2.10.2016)					
	51	0.1 [0.1; 0.2] 51 (100)	50	0.3 [0.2; 0.3] 50 (100)	
Cabozantinib vs everolimus (data cut-off from 2.10.2016)					
	331	n. d. 331 (100)	322	n. d. 321 (100)	

(continuation)

Endpoint	Lenvatinib + everolimus or cabozantinib		Everolimus (bridge comparator)		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Serious adverse events (SAEs)					
Lenvatinib + everolimus vs everolimus					
	51	11.9 [2.1; 19.4] 30 (58.8)	50	7.6 [5.7; n. a.] 21 (42.0)	1.18 [0.66; 2.10] n. d.
Cabozantinib vs everolimus (data cut-off from 2.10.2016)					
	331	12.9 [10.4; 18.2] 154 (47)	322	11.1 [7.5; 14.1] 144 (45)	0.80 [0.63; 1.00] 0.052
Adjusted indirect compare[b]: Lenvatinib + everolimus vs cabozantinib					1.48 [0.79; 2.75][c] n. d.
Severe adverse events (CTCAE grade ≥ 3)					
Lenvatinib + everolimus vs everolimus (data cut-off from 2.10.2016)					
	51	1.6 [0.9; 4.1] 39 (76.5)	50	5.8 [1.9; n. a.] 27 (54.0)	1.59 [0.96; 2.62] n. d.
Cabozantinib vs everolimus (data cut-off from 2.10.2016)					
	331	2.2 [1.7; 2.8] 264 (80)	322	3.6 [2.8; 4.6] 219 (68)	1.23 [1.03; 1.47] 0.023
Adjusted indirect compare[b]: Lenvatinib + everolimus vs cabozantinib					1.29 [0.76; 2.20][c] n. d.
Therapy discontinuation due to adverse events					
Lenvatinib + everolimus vs everolimus (data cut-off from 2.10.2016)					
	51	n. a. [24.4; n. a.] 13 (25.5)	50	n. a. [13.5; n. a.] 6 (12.0)	1.64 [0.62; 4.37] n. d.
Cabozantinib vs everolimus (data cut-off from 2.10.2016)					
	331	n. a. [27.5; n. c.] 88 (27)	322	26.2 [19.4; n. a.] 87 (27)	0.72 [0.54; 0.98] 0.036
Adjusted indirect compare[b]: Lenvatinib + everolimus vs cabozantinib					-[d]
Specific adverse events					
No usable data available[e]					

(continuation)

a Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b Indirect comparison according to Bucher
c Information from the dossier (module 4) of the pharmaceutical company
d No presentation of effect estimates due to insufficient certainty of results
e The pharmaceutical company submits only a selection of specific AEs for the indirect comparison

Abbreviations used:
Common Terminology Criteria for Adverse Events; HR = Hazard Ratio; n.d = no data; 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; SAE = serious adverse event; vs = versus.

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

approx. 1,770 to 3,530 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 Kisplyx (active ingredient: lenvatinib) at the following publicly accessible link (last access: 3 March 2021):
https://www.ema.europa.eu/en/documents/product-information/kisplyx-epar-product-information_de.pdf

Treatment with lenvatinib should only be initiated in patients with advanced renal cell carcinoma and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and in nephrology, and specialists participating in the Oncology Agreement.

Patients with brain metastases were not studied in the 205 study. Especially in these patients, a careful risk-benefit assessment must be made before starting therapy.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Lenvatinib	€ 51,559.17
Everolimus	€ 10,087.99
Total:	€ 61,647.16
Additional SHI services	Patient-individual
Appropriate comparator therapy:	
Nivolumab	€ 79,308.84 - € 79,613.87
Cabozantinib	€ 65,515.31

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 June 2021)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	13 - 26.1	€ 923 - € 1,853.10

II. The resolution will enter into force on the day of its publication on the internet on the G-BA website on 1 July 2021.

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

Berlin, 1 July 2021

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

Prof. Hecken