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
Lenvatinib (new therapeutic indication: endometrial carcinoma, after prior platinum-containing therapy, combination with pembrolizumab)

of 7 July 2022

At its session on 7 July 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 last 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 lenvatinib in accordance with the resolution of 1 July 2021:**

Lenvatinib

Resolution of: 7 July 2022
Entry into force on: 7 July 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 26 November 2021):

Lenvatinib in combination with pembrolizumab is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.

Therapeutic indication of the resolution (resolution of 7 July 2022):

See new therapeutic indication according to marketing authorisation.

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

Adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of lenvatinib in combination with pembrolizumab compared to the appropriate comparator therapy:

Indication of a considerable additional benefit

Study results according to endpoints:

Adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantages for dyspnoea, lymphoedema, tingling/ numbness, change in taste and hair loss, disadvantage for diarrhoea
Health-related quality of life	↔	In the overall assessment of all results, no relevant difference for the benefit assessment; a positive effect is shown for the endpoint "negative body image"
Side effects	↓↓	Disadvantages in the endpoints of serious AEs and therapy discontinuation due to AEs, in detail mainly disadvantages for specific AEs
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		

KEYNOTE 775 / 309 study: Lenvatinib + pembrolizumab **vs** therapy according to doctor's instructions under selection of doxorubicin or paclitaxel[1, 2]

Total population

Study design: randomised, open-label, actively controlled

[1] Data from the dossier assessment of the IQWiG (A21-162) and from the addendum (A22-57), unless otherwise indicated.
[2] Data cut-off from 26.10.2020

Mortality

Endpoint	**Lenvatinib + pembrolizumab**		**Therapy according to doctor's instructions (doxorubicin or paclitaxel)**		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					
	411	18.3 [15.2; 20.5] 188 (45.7)	416	11.4 [10.5; 12.9] 245 (58.9)	0.62 [0.51; 0.75] < 0.001 6.9 months

Morbidity

Endpoint	**Lenvatinib + pembrolizumab**		**Therapy according to doctor's instructions (doxorubicin or paclitaxel)**		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]					
	411	7.2 [5.7; 7.6] 281 (68.4)	416	3.8 [3.6; 4.2] 286 (68.8)	0.56 [0.47; 0.66] < 0.001 3.5 months

Endpoint	**Lenvatinib + pembrolizumab**			**Therapy according to doctor's instructions (doxorubicin or paclitaxel)**			Intervention vs control
	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	MD [95% CI] p value[d]
Disease symptomatology							
Symptom scales of the EORTC QLQ-C30[e]							
Fatigue	370	31.11 (22.53)	9.01 (0.84)	350	34.10 (25.56)	12.03 (0.95)	-3.02 [-5.41; -0.63]

Endpoint	Lenvatinib + pembrolizumab			Therapy according to doctor's instructions (doxorubicin or paclitaxel)			Intervention vs control
	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	MD [95% CI] p value[d]
							n.d. SMD: −0.18 [−0.33; −0.04][f]
Nausea and vomiting	370	8.69 (17.45)	5.49 (0.73)	350	9.29 (18.38)	8.07 (0.83)	-2.58 [−4.66; −0.50] n.d. SMD: −0.18 [−0.33; −0.03][f]
Pain	370	29.05 (27.53)	6.20 (0.95)	350	29.33 (28.57)	4.35 (1.06)	1.85 [−0.84; 4.53] n.d.
Dyspnoea	370	15.59 (22.90)	2.05 (0.83)	350	16.38 (23.90)	7.62 (0.92)	-5.58 [−7.91; −3.24] n.d. SMD: −0.35 [−0.50; −0.202][f]
Insomnia	370	24.50 (27.44)	1.53 (0.99)	350	28.38 (28.11)	4.32 (1.11)	-2.79 [−5.60; 0.02] n.d.
Appetite loss	370	20.45 (27.64)	12.95 (1.07)	350	21.24 (29.69)	8.51 (1.22)	4.44 [1.37; 7.51] n.d. SMD: 0.21 [0.06; 0.36][f]
Constipation	370	21.35 (28.47)	-1.23 (0.95)	350	23.05 (30.94)	2.67 (1.07)	-3.90 [−6.60; −1.20] n.d. SMD: −0.21 [−0.36; −0.06][f]
Diarrhoea	370	6.94 (17.09)	11.15 (0.80)	350	7.43 (17.54)	5.38 (0.94)	5.77 [3.44; 8.10] n.d. SMD: 0.36 [0.21; 0.51][f]
Symptom scales of the EORTC QLQ-EN24[e]							
Lymphoedema	308	17.42 (26.38)	2.61 (1.00)	297	16.67 (24.00)	9.21 (1.10)	-6.60

Endpoint	Lenvatinib + pembrolizumab			Therapy according to doctor's instructions (doxorubicin or paclitaxel)			Intervention vs control
	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	MD [95% CI] p value[d]
							[−9.37; −3.82] n.d. SMD: −0.38 [−0.54; −0.22][f]
Urological symptoms	308	14.94 (17.95)	-0.93 (0.69)	297	16.13 (19.40)	2.24 (0.75)	-3.17 [−5.07; −1.27] n.d. SMD: −0.27 [−0.43; −0.11][f]
Gastrointestinal symptoms	308	12.64 (14.11)	3.24 (0.58)	297	14.55 (14.65)	2.81 (0.65)	0.43 [−1.19; 2.05] n.d.
Sexual/ vaginal problems	no usable data available[g]						
Back and pelvic pain	308	29.22 (29.68)	-0.69 (1.02)	297	31.76 (31.20)	1.52 (1.15)	-2.21 [−5.09; 0.67] n.d.
Tingling/ numbness	308	30.84 (30.63)	-3.33 (1.12)	297	27.05 (29.47)	3.81 (1.23)	-7.15 [-10.27; -4.03] n.d. SMD: −0.36 [−0.53; −0.204][f]
Muscular pain	308	23.16 (26.59)	8.69 (1.12)	297	21.89 (27.87)	2.32 (1.25)	6.37 [3.22; 9.52] n.d. SMD: 0.32 [0.16; 0.48][f]
Hair loss	308	15.37 (32.09)	-4.44 (1.25)	297	17.28 (34.67)	53.60 (1.39)	-58.03 [-61.54; -54.53] n.d. SMD: −2.64 [−2.85; −2.42][f]
Change of taste	308	11.47 (22.95)	14.31 (1.27)	297	15.60 (26.56)	23.90 (1.41)	-9.59 [-13.14; -6.04] n.d. SMD: −0.43 [−0.59; −0.27][f]
Health status							

Endpoint	Lenvatinib + pembrolizumab			Therapy according to doctor's instructions (doxorubicin or paclitaxel)			Intervention vs control
	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	MD [95% CI] p value[d]
EQ-5D VAS[h]							
	375	73.70 (18.24)	-4.99 (0.70)	356	73.53 (18.91)	-7.61 (0.76)	2.62 [0.67; 4.57] n.d. SMD: 0.19 [0.05; 0.34][f]

Health-related quality of life

Endpoint	Lenvatinib + pembrolizumab			Therapy according to doctor's instructions (doxorubicin or paclitaxel)			Intervention vs control
	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	MD [95% CI] p value[d]
Health-related quality of life							
Functional scales of the EORTC QLQ-C30[h]							
Global health status	370	65.74 (21.87)	-6.58 (0.76)	350	65.64 (22.72)	-8.03 (0.85)	1.45 [−0.69; 3.60] n.d.
Physical functioning	370	78.68 (20.08)	-9.51 (0.76)	350	75.94 (20.90)	-9.24 (0.84)	-0.27 [−2.41; 1.86] n.d.
Role functioning	370	78.38 (25.46)	-11.67 (0.99)	350	75.62 (27.83)	-11.92 (1.09)	0.24 [−2.53; 3.02] n.d.
Emotional functioning	370	75.83 (19.85)	1.34 (0.76)	350	73.48 (21.68)	-2.17 (0.83)	3.51 [1.38; 5.64] n.d. SMD: 0.24 [0.09; 0.39][f]
Cognitive functioning	370	84.28 (19.59)	-3.56 (0.76)	350	83.76 (18.43)	-5.23 (0.82)	1.68 [−0.44; 3.79] n.d.

Endpoint	Lenvatinib + pembrolizumab			Therapy according to doctor's instructions (doxorubicin or paclitaxel)			Intervention vs control
	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	N[c]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)[d]	MD [95% CI] p value[d]
Social functioning	370	79.59 (23.80)	-6.99 (1.00)	350	78.57 (25.10)	-10.26 (1.09)	3.27 [0.48; 6.05] n.d. SMD: 0.17 [0.03; 0.32][f]
Functional scales of the EORTC QLQ-EN24							
Libido[h]	306	8.28 (17.61)	-3.45 (0.54)	290	8.28 (17.11)	-4.24 (0.60)	0.79 [−0.72; 2.29] n.d.
Sexual activity[h]	302	7.40 (15.86)	-3.63 (0.45)	289	5.88 (14.16)	-3.73 (0.50)	0.11 [−1.16; 1.37] n.d.
Sexual pleasure	no usable data available[g]						
Negative body image[e, i]	308	22.40 (28.24)	1.51 (1.28)	297	24.80 (29.39)	13.23 (1.36)	-11.73 [-15.23; -8.22] n.d. SMD: −0.53 [−0.69; −0.37][f]

Side effects

Endpoint	Lenvatinib + pembrolizumab		Therapy according to doctor's instructions (doxorubicin or paclitaxel)		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]
Adverse events (AEs) presented additionally[j]					
	406	0.6 [0.4; 0.7] 405 (99.8)	388	0.6 [0.4; 0.7] 386 (99.5)	-
Serious adverse events (SAE)[j]					
	406	40.9 [30.0; 53.6] 214 (52.7)	388	n.a. [55.7; n.a.] 118 (30.4)	1.67 [1.33; 2.09] n.d.
Severe adverse events (CTCAE grade ≥ 3)[j]					
	406	5.1 [3.9; 6.3] 361 (88.9)	388	3.6 [2.3; 5.1] 282 (72.7)	1.07 [0.91; 1.25] n.d.
Therapy discontinuation due to adverse events[j, k]					
	406	n.a. [77,4; -] 134 (33.0)	388	n.a. [59.1; n.a.] 31 (8.0)	2.81 [1.89; 4.20] n.d.
Specific adverse events					
Immune-mediated SAEs[l]	406	n.a. 41 (10.1)	388	n.a. 1 (0.3)	29.55 [4.05; 215.69] n.d.
Immune-mediated severe AEs[l]	406	n.a. 53 (13.1)	388	n.a. 1 (0.3)	29.93 [4.11; 217.76] n.d.
Hypertension (PT, severe AEs)	406	n.a. 154 (37.9)	388	n.a. 9 (2.3)	17.49 [8.92; 34.30] n.d.
Haemorrhage	no usable data available[m]				
Cardiotoxicity (operationalised as SOC heart disease, severe AEs)	406	n.a. 11 (2.7)	388	n.a. 12 (3.1)	0.42 [0.17; 1.00] n.d.

Endpoint	**Lenvatinib + pembrolizumab**		**Therapy according to doctor's instructions (doxorubicin or paclitaxel)**		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]
Headache (PT, AEs)	406	n.a. 101 (24.9)	388	n.a. 34 (8.8)	2.59 [1.75; 3.84] n.d.
Alopecia (PT, AEs)	406	n.a. 22 (5.4)	388	n.a. 120 (30.9)	0.12 [0.07; 0.18] n.d.
Urinary tract infection (PT, SAEs)	406	n.a. 13 (3.2)	388	n.a. 2 (0.5)	5.04 [1.13; 22.58] n.d.
Blood and lymphatic system disorders (SOC, severe AEs)	406	n.a. 45 (11.1)	388	n.a. [25.9; n.a.] 159 (41.0)	0.18 [0.13; 0.26] n.d.
Gastrointestinal disorders (SOC, severe AEs)	406	n.a. [85.4; n.a.] 106 (26.1)	388	n.a. 41 (10.6)	1.63 [1.12; 2.37] n.d.
Hepatobiliary disorders (SOC, severe AEs)	406	n.a. 27 (6.7)	388	n.a. 1 (0.3)	13.95 [1.87; 103.91] n.d.
Lipase elevated (PT, severe AEs)	406	n.a. 26 (6.4)	388	n.a. 5 (1.3)	3.08 [1.15; 8.29] n.d.
Weight loss (PT, severe AEs)	406	n.a. 42 (10.3)	388	n.a. 1 (0.3)	16.29 [2.21; 119.86] n.d.
Metabolism and nutrition disorders (SOC, severe AEs)	406	n.a. 97 (23.9)	388	n.a. 27 (7.0)	2.44 [1.58; 3.77] n.d.
Musculoskeletal and connective tissue disorders (SOC, severe AEs)	406	n.a. 30 (7.4)	388	n.a. 5 (1.3)	3.65 [1.39; 9.57] n.d.
Proteinuria (PT, severe AEs)	406	n.a. 22 (5.4)	388	n.a. 1 (0.3)	16.16 [2.16; 120.89] n.d.

Endpoint	Lenvatinib + pembrolizumab		Therapy according to doctor's instructions (doxorubicin or paclitaxel)		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]
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs)	406	n.a. 20 (4.9)	388	n.a. 26 (6.7)	0.44 [0.23; 0.82] n.d.
Palmar-plantar erythrodysesthesia syndrome (PT, severe AEs)	406	n.a. 11 (2.7)	388	n.a. 0 (0.0)	n.d. n.d.

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Data from: Written statement by the pharmaceutical company on lenvatinib dated 09.05.2022
[c] Number of patients included in the evaluation for the calculation of the effect estimate, values at the start of the study may be based on other patient numbers.
[d] From MMRM; effect represents the difference between the treatment groups of the changes averaged over the course of the study between the respective time of measurement and the start of the study.
[e] Higher values on the respective scale correspond to worse symptomatology, a positive group difference means a disadvantage for lenvatinib + pembrolizumab.
[f] IQWiG calculation
[g] Approximately 82% of the patients were not included in the analyses
[h] Higher scores on the respective scale correspond to a better health status or a better health-related quality of life, a positive group difference means an advantage for lenvatinib + pembrolizumab.
[i] In deviation from the pharmaceutical company's recommendation, this scale was not assigned to symptomatology, but to health-related quality of life.
[j] According to information in the study report without recording the progression of the underlying disease
[k] Discontinuation of at least 1 active ingredient component in the intervention arm
[l] In each case, the operationalisation of the pharmaceutical company specific MedDRA PT collection from the endpoint Adverse Events Of Special Interest (AEOSI) was used.
[m] No suitable operationalisation available.

Abbreviations used:
AD = absolute difference; AEOSI = adverse events of special interest; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; n.d. = no data available; CI = confidence interval; MD = mean difference; MedDRA = Medical Dictionary of Drug Regulatory Activities; MMRM = Mixed Model with Repeated Measures; MV = mean value; 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; QLQ-EN24 = Quality of Life Questionnaire - Endometrial Cancer Module 24; QLQ-C30 = Quality of Life Questionnaire - Core 30; SD = standard deviation; SE = standard error; SMD = standardised mean difference; SOC = system organ class; VAS = visual analogue scale; vs = versus

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

Adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation

approx. 1,130 – 5,070 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 Lenvima (active ingredient: lenvatinib) at the following publicly accessible link (last access: 5 May 2022):

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

Therapy with lenvatinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with endometrial carcinoma.

In the KEYNOTE 775 / 309 study, treatment with lenvatinib in combination with pembrolizumab was compared with treatment according to doctor's instructions under selection of doxorubicin or paclitaxel only. No comparison was made with other treatment options.

4. Treatment costs

Annual treatment costs:

Adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lenvatinib in combination with pembrolizumab	
Lenvatinib	€ 42,561.92
Pembrolizumab	€ 99,714.53
Total:	€ 142,276.45
Best supportive care	Different from patient to patient

Designation of the therapy	Annual treatment costs/ patient
Appropriate comparator therapy:	
Therapy according to doctor's instructions[a]	
Medroxyprogesterone acetate	€ 714.31 - € 1,222.35
Megestrol acetate	€ 2,366.26 – € 9,465.06
Cisplatin monotherapy	€ 931.84 – € 3,594.84
Additionally required SHI services	€ 245.49 - € 2,108.10
Doxorubicin monotherapy	€ 2,089.43 - € 2,690.52
Cisplatin + doxorubicin	
Cisplatin	€ 430.08
Doxorubicin	€ 1,790.94
Total:	€ 2,221.02
Additionally required SHI services	€ 156.26 - € 188.84
Best supportive care	Different from patient to patient
[a] The active ingredients carboplatin and paclitaxel are suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.	

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2022)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.7 - 17.4	€ 617.70 - € 1,235.40
Cisplatin (monotherapy)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1 or 5	13.0 - 17.4 or 65.0 – 87.0	€ 1,053.00 - € 1,409.40 or € 5,265.00 - € 7,047.00
Cisplatin (in combination with doxorubicin)	Surcharge for production of a parenteral preparation	€ 81	1	6	€ 486

	containing cytostatic agents				
Doxorubicin (monotherapy)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Doxorubicin (in combination with cisplatin)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	6	€ 486

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 7 July 2022.

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

Berlin, 7 July 2022

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

Prof. Hecken