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)
Elacestrant (breast cancer, ER+, HER2-, with ESR1 mutation, after at least 1 prior therapy)

of 2 May 2024

At its session on 2 May 2024, 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. Annex XII shall be amended in alphabetical order to include the active ingredient Elacestrant as follows:

Elacestrant

Resolution of: 2 May 2024
Entry into force on: 2 May 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 15 September 2023):

ORSERDU monotherapy is indicated for the treatment of postmenopausal women, and men, with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

Therapeutic indication of the resolution (resolution of 2 May 2024):

See therapeutic indication according to marketing authorisation.

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

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

Appropriate comparator therapy:

Therapy according to doctor's instructions, taking into account a change of endocrine therapy to

- tamoxifen
- anastrozole
- fulvestrant as monotherapy
- letrozole
- exemestane
- everolimus in combination with exemestane (only for patients without symptomatic visceral metastasis, followed by progression after a non-steroidal aromatase inhibitor).

Extent and probability of the additional benefit of elacestrant compared to therapy according to doctor's instructions:

a1) Postmenopausal women with 1 prior line of endocrine therapy

An additional benefit is not proven.

a2) Postmenopausal women with 2 prior lines of endocrine therapy

Hint for a considerable additional benefit.

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

Appropriate comparator therapy:

Therapy according to doctor's instructions, taking into account a change of endocrine therapy to

- tamoxifen,
- aromatase inhibitor in combination with a GnRH analogue,
- fulvestrant

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

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

1 Data from the dossier assessment of the IQWiG (A23-104) and from the addendum (A24-30), unless otherwise indicated.

a1) Postmenopausal women with 1 prior line of endocrine therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	There is no relevant difference for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment overall. In detail, disadvantage in the endpoint of appetite loss and advantage in the endpoint of insomnia.
Health-related quality of life	↔	There is no relevant difference for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment overall. Detailed disadvantages in the specific AEs "gastrointestinal disorders" and "musculoskeletal and connective tissue disorders"

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
∅: No data available.
n.a.: not assessable

a2) Postmenopausal women with 2 prior lines of endocrine therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	↔	No relevant differences for the benefit assessment overall. In detail, disadvantage in the endpoint of appetite loss.
Health-related quality of life	↔	There is no relevant difference for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment overall. Detailed disadvantages in the specific AEs "gastrointestinal disorders" and "musculoskeletal and connective tissue disorders"
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 ∅: No data available. n.a.: not assessable		

EMERALD study:

- open-label, randomised phase III study
- Elacestrant vs therapy according to doctor's instructions with a choice of fulvestrant, anastrozole, letrozole and exemestane
- Relevant sub-population: ESR1 mutated patients
- Relevant data cut-offs:
  Data cut-off from 08.07.2022 (morbidity, health-related quality of life, side effects)
  Data cut-off from 02.09.2022 (mortality)

Mortality

	Elacestrant		Therapy according to doctor's instructions[a]		Elacestrant vs therapy according to doctor's instructions[a]
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N[b]	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[c]
Overall survival					
	115	24.2 [20.5; 28.7] *61 (53.0)*	113	23.5 [15.6; 29.9] *60 (53.1)*	0.90 [0.63; 1.30] 0.582
Effect modification by the characteristic number of previous endocrine therapy lines in the advanced/ metastatic stage					
1	73	24.2 [18.3; 31.9] *38 (52.1)*	69	29.9 [21.3; n.c.] *29 (42.0)*	1.34 [0.82; 2.21] 0.239
2	42	26.3 [19.8; 33.0] *23 (54.8)*	44	15.6 [12.2; 19.8] *31 (70.5)*	0.50 [0.28; 0.852] 0.010 AD: 10.7 months
				Interaction:	0.008

Morbidity

	Elacestrant		Therapy according to doctor's instructions[a]		Elacestrant vs therapy according to doctor's instructions[a]
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N[b]	Median time to event in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[c]
Progression-free survival (PFS)[d]					
	115	3.78 [2.17; 7.26] *67 (58.3)*	113	1.87 [1.87; 2.14] *80 (70.8)*	0.54 [0.38; 0.76] 0.0004 AD: 1.91 months
Symptomatology (EORTC QLQ-C30[e])					
Fatigue	115	1.5 [1.0; 2.0] *59 (51.3)*	113	1.5 [1.0; 2.8] *55 (48.7)*	0.87 [0.59; 1.27] 0.462
Nausea/ vomiting	115	1.1 [1.0; 1.9] *61 (53.0)*	113	2.1 [1.9; 3.3] *31 (27.4)*	1.46 [0.94; 2.31] 0.101
Pain	115	1.9 [1.0; 2.8] *66 (57.4)*	113	1.9 [1.0; 2.8] *48 (42.5)*	1.09 [0.74; 1.62] 0.659
Dyspnoea	115	3.1 [1.9; 8.3] *37 (32.2)*	113	2.8 [1.9; 3.8] *39 (34.5)*	0.74 [0.47; 1.18] 0.233
Insomnia	115	4.0 [2.0; 8.5] *45 (39.1)*	113	2.0 [1.9; 2.9] *44 (38.9)*	0.74 [0.48; 1.14] 0.178
Effect modification by the characteristic number of previous endocrine therapy lines in the advanced/ metastatic stage					
1	73	6.5 [2.3; 12.8] *25 (34.2)*	69	1.5 [1.0; 2.8] *29 (42.0)*	0.43 [0.25; 0.75] 0.002 AD: 5 months
2	42	1.9 [0.9; 19.1] *20 (47.6)*	44	2.8 [2.0; n.c.] *15 (34.1)*	1.41 [0.71; 2.84] 0.309
				Interaction:	0.012

	Elacestrant		Therapy according to doctor's instructions[a]		Elacestrant vs therapy according to doctor's instructions[a]
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N[b]	Median time to event in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[c]
Appetite loss	115	2.3 [1.8; 4.7] *51 (44.3)*	113	3.9 [2.8; 6.3] *25 (22.1)*	1.84 [1.12; 3.11] 0.018 AD: 1.6 months
Constipation	115	4.9 [2.8; 8.4] *33 (28.7)*	113	3.0 [2.8; 4.7] *34 (30.1)*	0.72 [0.44; 1.18] 0.172
Diarrhoea	115	8.3 [2.3; n.c.] *32 (27.8)*	113	3.4 [2.8; 5.9] *26 (23.0)*	0.97 [0.57; 1.68] 0.901
Health status (EQ-5D VAS[f])					
	115	8.3 [4.8; n.c.] *37 (32.2)*	113	10.3 [5.9; n.c.] *31 (27.4)*	0.93 [0.57; 1.52] 0.751

Health-related quality of life

	Elacestrant		Therapy according to doctor's instructions[a]		Elacestrant vs therapy according to doctor's instructions[a]
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N[b]	Median time to event in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value
EORTC QLQ-C30[g]					
Global health status	115	3.7 [2.3; 6.5] *54 (47.0)*	113	2.1 [1.5; 4.7] *39 (34.5)*	0.75 [0.49; 1.17] 0.190
Physical functioning	115	2.8 [1.9; 4.7] *49 (42.6)*	113	2.8 [1.9; 4.7] *36 (31.9)*	0.96 [0.62; 1.51] 0.916
Role functioning	115	1.9 [1.0; 3.9] *62 (53.9)*	113	2.8 [1.9; 5.9] *35 (31.0)*	1.23 [0.81; 1.89] 0.347
Emotional functioning	115	6.5 [2.8; 8.4] *40 (34.8)*	113	2.9 [2.8; 5.9] *30 (26.5)*	0.88 [0.53; 1.48] 0.627
Cognitive functioning	115	4.0 [2.3; 8.3] *46 (40.0)*	113	2.8 [2.2; 3.5] *35 (31.0)*	0.99 [0.62; 1.60] 0.944
Social functioning	115	3.9 [1.9; 6.6] *49 (42.6)*	113	2.2 [1.0; 3.0] *42 (37.2)*	0.78 [0.50; 1.22] 0.267

Side effects

	Elacestrant		Therapy according to doctor's instructions[a]		Elacestrant vs therapy according to doctor's instructions[a]
	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 (%)*	Effect estimator [95% CI] p value
Total adverse events (presented additionally)					
	115	0.3 [0.1; 0.5] *105 (91.3)*	106	0.5 [0.3; 0.5] *92 (86.8)*	-
Serious adverse events (SAE)					
	115	n.r. *14 (12.2)*	106	n.r. *12 (11.3)*	0.85 [0.39; 1.88] 0.678
Severe adverse events (CTCAE grade ≥ 3)					
	115	n.r. *33 (28.7)*	106	13.1 [13.1; n.c.] *24 (22.6)*	1.11 [0.66; 1.90] 0.701
Therapy discontinuation due to adverse events					
	115	n.r. *6 (5.2)*	106	n.r. *4 (3.8)*	1.28 [0.36; 5.03] 0.701
Specific adverse events					
Gastrointestinal disorders (SOC, AEs)	115	1.8 [1.0; 2.7] *75 (65.2)*	106	n.r. [5.9; n.c.] *33 (31.1)*	2.56 [1.71; 3.92] < 0.001
Musculoskeletal and connective tissue disorders (SOC, severe AEs)	115	n.r. *10 (8.7)*	106	n.r. *1 (0.9)*	7.41 [1.40; 136.55] 0.026

[a] Fulvestrant, anastrozole, letrozole or exemestane of the doctor's choice
[b] For the endpoints of mortality, morbidity and health-related quality of life, 113 patients were formally enrolled in the evaluation, but since 7 patients withdrew their consent before the first study medication was administered, it is assumed that they were censored at baseline and are therefore enrolled in the evaluation without any information.
[c] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[d] Information of the pharmaceutical company
[e] Time to first deterioration; an increase in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (range of values of the scale: 0 to 100).
[f] Time to first deterioration; a decrease in score by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (range of values of the scale: 0 to 100).
[g] Time to first deterioration; a decrease in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (range of values of the scale: 0 to 100).

	Elacestrant		Therapy according to doctor's instructions[a]		Elacestrant vs therapy according to doctor's instructions[a]
	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 (%)*	Effect estimator [95% CI] p value
Abbreviations used: AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; 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.r. = not reached; QLQ-C30 = Quality of Life Questionnaire – Core 30; SOC = system organ class; VAS = visual analogue scale; vs = versus					

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

No data are available to allow an assessment of the additional benefit.

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 ∅: No data available. n.a.: not assessable		

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

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

a1) Postmenopausal women with 1 prior line of endocrine therapy

approx. 920 - 9,630 patients

a2) Postmenopausal women with 2 prior lines of endocrine therapy

approx. 590 - 6,260 patients

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

approx. 17 – 180 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 Orserdu (active ingredient: elacestrant) at the following publicly accessible link (last access: 22 January 2024):

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

Treatment with elacestrant should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, obstetrics and gynaecology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with locally advanced or metastatic breast cancer.

Patients should be selected for treatment with ORSERDU based on the presence of an activating ESR1 mutation in plasma specimens, using a CE-marked in vitro diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, the presence of an activating ESR1 mutation in plasma specimens should be assessed by an alternative validated test.

4. Treatment costs

Annual treatment costs:

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Elacestrant	€ 128,781.26
Appropriate comparator therapy:	
Tamoxifen	
Tamoxifen	€ 71.50
Anastrozole	
Anastrozole	€ 133.53
Fulvestrant	
Fulvestrant	€ 4,416.88
Letrozole	
Letrozole	€ 169.42
Exemestane	
Exemestane	€ 424.64
Everolimus	
Everolimus	€ 5,769.31
Everolimus in combination with exemestane	€ 6,193.95

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2024)

Costs for additionally required SHI services: not applicable

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Elacestrant	€ 128,781.26
Appropriate comparator therapy:	
Tamoxifen	
Tamoxifen	€ 71.50
Fulvestrant	
Fulvestrant	€ 2,378.32
Aromatase inhibitor in combination with a GnRH analogue	
Aromatase inhibitors	€ 133.53 - € 424.64
GnRH analogues	€ 2,048.41 - € 2,581.76
Total	€ 2,217.83 - € 3,006.40[2]

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2024)

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

2 The range is based on the combinations of active ingredients referenced in the publication by DiLauro et al. (2015): letrozole and leuprorelin (lower limit) and exemestane and goserlin (upper limit): Di Lauro et al. Role of gonadotropin-releasing hormone analogues in metastatic male breast cancer: results from a pooled analysis. J Hematol Oncol. 2015 May 17;8:53

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 2 May 2024.

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

Berlin, 2 May 2024

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

Prof. Hecken