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
Trastuzumab deruxtecan (breast cancer, HER2+, at least 2 prior therapies)

of 2 February 2023

At its session on 2 February 2023, 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 Trastuzumab deruxtecan as follows:

Trastuzumab deruxtecan

Resolution of: 2 February 2023
Entry into force on: 2 February 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 18 January 2022):

Trastuzumab deruxtecan (Enhertu) as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.

Therapeutic indication (according to the marketing authorisation of 11 July 2022):

Trastuzumab deruxtecan (Enhertu®) as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

Therapeutic indication of the resolution (resolution of 2 February 2023):

Trastuzumab deruxtecan (Enhertu) as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.

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

Adult patients with HER2-positive unresectable or metastatic breast cancer previously treated with two or more anti-HER2 based therapies

Appropriate comparator therapy:

- Therapy according to doctor's instructions

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

Indication of a considerable additional benefit

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantages in the endpoints health status, pain, insomnia, diarrhoea, symptoms in the chest and arms; disadvantages in the endpoints constipation, nausea and vomiting; overall an advantage
Health-related quality of life	↑	Advantages in the endpoints of global health status, physical, cognitive, and social functioning, and role functioning
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.c.: not calculable		

[1] Data from the dossier assessment of the IQWiG (A22-81) and from the addendum (A22-127), unless otherwise indicated.

DESTINY-Breast02 study: Trastuzumab deruxtecan **vs** therapy according to doctor's instructions (trastuzumab + capecitabine, lapatinib + capecitabine)

Study design: ongoing, open-label, controlled, randomised, two-arm phase III study

Mortality

Endpoint	**Trastuzumab deruxtecan**		**Therapy according to doctor's instructions**		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[b] Absolute difference (AD)[a]
Overall survival					
	406	39.2 [32.7; n.c.] 143 (35.2)	202	26.5 [21.0; n.c.] 86 (42.6)	0.66 [0.50; 0.86] 0.002 AD: + 12.7 months

Morbidity

Endpoint	**Trastuzumab deruxtecan**		**Therapy according to doctor's instructions**		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[b] Absolute difference (AD)[a]
Progression-free survival (PFS)[i]					
	406	17.8 [14.3; 20.8]	202	6.9 [5.5; 8.4]	0.3589 [0.2840; 0.4535] < 0.0001 AD: + 10.9 months
Symptom scales of the EORTC QLQ-C30[c]					
Fatigue	406	2.9 [2.8; 4.2] 279 (68.7)	202	1.9 [1.5; 2.9] 129 (63.9)	0.82 [0.66; 1.01] 0.060
Nausea and vomiting	406	1.5 [1.5; 1.8] 296 (72.9)	202	3.0 [1.7; 4.4] 111 (55.0)	1.30 [1.04; 1.62] 0.022 AD: - 1.5 months

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions		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[b] Absolute difference (AD)[a]
Pain	406	8.5 [6.0; 11.2] 222 (54.7)	202	2.8 [1.9; 3.5] 117 (57.9)	0.58 [0.46; 0.73] < 0.001 AD: + 5.7 months
Dyspnoea	406	15.6 [12.6; 21.7] 180 (44.3)	202	11.6 [8.0; n.c.] 74 (36.6)	0.86 [0.65; 1.13] 0.286
Insomnia	406	13.4 [9.9; 16.7] 193 (47.5)	202	5.8 [4.3; 9.2] 91 (45.0)	0.68 [0.52; 0.87] 0.003 AD: + 7.6 months
Appetite loss	406	5.5 [3.0; 7.3] 252 (62.1)	202	2.9 [1.7; 4.4] 108 (53.5)	0.83 [0.66; 1.04] 0.107
Constipation	406	5.5 [4.3; 6.3] 251 (61.8)	202	18.7 [8.1; n.c.] 69 (34.2)	1.62 [1.24; 2.13] < 0.001 AD: - 13.2 months
Diarrhoea	406	9.7 [7.8; 13.0] 218 (53.7)	202	1.5 [1.5; 1.8] 128 (63.4)	0.40 [0.32; 0.51] < 0.001 AD: + 8.2 months
Symptom scales of the EORTC QLQ-BR23[c]					
Side effects of systemic therapy	406	5.1 [4.2; 6.9] 239 (58.9)	202	5.8 [3.3; 1.26] 90 (44.6)	1.07 [0.84; 1.37] 0.613
Symptoms in the chest	406	n.a. [27.8; n.c.] 109 (26.8)	202	18.4 [12.5; n.c.] 60 (29.7)	0.58 [0.42; 0.81] 0.001
Endpoint	**Trastuzumab deruxtecan**		**Therapy according to doctor's instructions**		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[b] Absolute difference (AD)[a]
Arm symptoms	406	10.0 [6.9; 13.9] 206 (50.7)	202	4.4 [2.8; 6.1] 102 (50.5)	0.62 [0.48; 0.79] < 0.001 AD: + 5.6 months
Burden due to hair loss	No usable data available[d]				
Health status (EQ-5D VAS)[e]					
	406	19.4 [17.1; 24.9] 158 (38.9)	202	7.3 [5.6; 11.3] 85 (42.1)	0.56 [0.43; 0.74] < 0.001 AD: + 12.1 months

Health-related quality of life

Endpoint	**Trastuzumab deruxtecan**		**Therapy according to doctor's instructions**		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[b] Absolute difference (AD)[a]
Global health status and functional scales of the EORTC QLQ-C30[f]					
Global health status	406	7.0 [5.0; 10.0] 232 (57.1)	202	2.9 [1.9; 4.2] 123 (60.9)	0.58 [0.46; 0.72] < 0.001 AD: + 4.1 months
Physical functioning	406	11.4 [8.6; 15.4] 211 (52.0)	202	4.3 [3.1; 6.0] 109 (54.0)	0.61 [0.48; 0.79] < 0.001 AD: + 7.1 months
Endpoint	**Trastuzumab deruxtecan**		**Therapy according to doctor's instructions**		Intervention vs control
	N	Median time to event in months [95% CI]	N	Median time to event in months [95% CI]	Hazard ratio [95% CI] p value[b] Absolute difference (AD)[a]

		Patients with event n (%)		*Patients with event n (%)*	
Role functioning	406	5.6 [4.3; 8.6] 240 (59.1)	202	2.9 [1.8; 4.2] 116 (57.4)	0.68 [0.54; 0.86] < 0.001 AD: + 2.7 months
Emotional functioning	406	10.2 [7.9; 13.9] 206 (50.7)	202	7.2 [5.5; 10.6] 86 (42.6)	0.91 [0.70; 1.17] 0.453
Cognitive functioning	406	6.9 [5.5; 9.7] 229 (56.4)	202	3.3 [2.8; 5.7] 111 (55.0)	0.71 [0.56; 0.898] 0.004 AD: + 3.6 months
Social functioning	406	7.2 [5.6; 10.4] 225 (55.4)	202	3.3 [1.9; 6.1] 109 (54.0)	0.72 [0.57; 0.91] 0.005 AD: + 3.9 months
Functional scales of the EORTC QLQ-BR23[f]					
Body image	406	13.5 [8.1; 22.9] 187 (46.1)	202	10.6 [5.5; 17.1] 75 (37.1)	0.91 [0.69; 1.20] 0.507
Sexual activity	406	n.a. 110 (27.1)	202	n.a. 44 (21.8)	1.07 [0.75; 1.53] 0.700
Sex pleasure	No usable data available				
Future prospects	406	32.5 [20.7; n.c.] 158 (38.9)	202	12.5 [6.9; n.c.] 71 (35.1)	0.82 [0.62; 1.09] 0.170

Side effects

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions		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[b] Absolute difference (AD)[a]
Total adverse events (presented additionally)[g]					
	404	0.1 [0.1; 0.1] 403 (99.8)	195	0.2 [0.2; 0.3] 185 (94.9)	-
Serious adverse events (SAEs)[g]					
	404	n.a. [35.4; n.c.] 103 (25.5)	195	n.a. [15.7; n.c.] 46 (23.6)	0.70 [0.49; 0.9994] 0.049
Severe adverse events (CTCAE grade ≥ 3)[g]					
	404	11.0 [7.0; 16.3] 213 (52.7)	195	9.9 [5.1; 15.7] 86 (44.1)	0.92 [0.71; 1.18] 0.493
Discontinuation due to AEs[g]					
	404	n.a. 80 (19.8)	195	n.a. 19 (9.7)	1.08 [0.65; 1.81] 0.757
Specific adverse events					
Diarrhoea (PT, severe AE)	404	n.a. 11 (2.7)	195	n.a. 14 (7.2)	0.23 [0.10; 0.54] < 0.001
Cardiac disorders (SOC, severe AE)	404	n.d. 2 (0.5)	195	n.d. 4 (2.1)	-[h]
Palmar-plantar erythrodysesthesia syndrome (PT, severe AE)	404	n.a. 1 (0.2)	195	n.a. 20 (10.3)	0.02 [0.003; 0.14] < 0.001
Other specific AEs					
Asthenia (PT, severe AE)	404	n.a. 20 (5.0)	195	n.a. 1 (0.5)	7.92 [1.06; 59.23] 0.017

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions		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[b] Absolute difference (AD)[a]
Fatigue (PT, severe AE)	404	n.a. 16 (4.0)	195	n.a. 1 (0.5)	6.48 [0.86; 49.03] 0.038
Leukopenia (PT, severe AE)	404	n.a. 21 (5.2)	195	n.a. 0 (0)	n.a. [0.00; n.c.] 0.007
Neutropenia (PT, severe AE)	404	n.a. 43 (10.6)	195	n.a. 4 (2.1)	3.93 [1.40; 11.02] 0.005
Nausea (PT, AE)	404	0.2 [0.2; 0.4] 293 (72.5)	195	n.a. [12.1; n.c.] 73 (37.4)	2.70 [2.09; 3.50] < 0.001
Vomiting (PT, AE)	404	n.a. [24.0; n.c.] 152 (37.6)	195	n.a. 25 (12.8)	2.89 [1.89; 4.42] < 0.001
Constipation (PT, AE)	404	n.a. [22.8; n.c.] 142 (35.1)	195	n.a. 21 (10.8)	2.93 [1.85; 4.64] < 0.001
Stomatitis (PT, AE)	404	n.a. 45 (11.1)	195	n.a. 36 (18.5)	0.36 [0.23; 0.58] < 0.001
Alopecia (PT, AE)	404	n.a. 150 (37.1)	195	n.a. 8 (4.1)	9.72 [4.77; 19.81] < 0.001
Skin rash (PT, AE)	404	n.a. 27 (6.7)	195	n.a. 22 (11.3)	0.45 [0.25; 0.798] 0.005
Headache (PT, AE)	404	n.a. [38.9; n.c.] 80 (19.8)	195	n.a. 12 (6.2)	2.55 [1.38; 4.71] 0.002

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] Cox proportional hazards model (HR, 95% CI) and log-rank test (p-value) stratified by hormone-receptor status (positive/negative), previous treatment with pertuzumab (yes/no) and history of visceral disease (yes/no)
[c] Time to first deterioration. An increase by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[d] Unclear proportion of patients with missing values at the start of the study and during the course of the study
[e] Time to first deterioration. A decrease by ≥ 15 points compared to study design is considered a clinically relevant deterioration (scale range 0 to 100)

[f] Time to first deterioration. A decrease by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100)
[g] The pharmaceutical company presents evaluations including progression of the underlying disease for endpoints in the category of side effects.
[h] The pharmaceutical company does not provide any calculations on the HR, CI and p-value.
[i] Information from the dossier of the pharmaceutical company

Abbreviations used:
AD = absolute difference; 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; MedDRA = Medical Dictionary for Regulatory Activities; 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; PC = pharmaceutical company; QLQ-BR23 = Quality of Life Questionnaire – Breast Cancer 23; QLQ-C30 = Quality of Life Questionnaire – Core 30; RCT = randomised controlled trial; AE = adverse event; VAS = visual analogue scale; vs = versus

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

Approx. 1,350 to 1,640 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 Enhertu (active ingredient: trastuzumab deruxtecan) at the following publicly accessible link (last access: 21 November 2022):

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

Treatment with trastuzumab deruxtecan should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, obstetrics and gynaecology, and specialists participating in the Oncology Agreement are experienced in the treatment of adults with breast cancer.

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:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Trastuzumab deruxtecan	€ 151,314.58
Appropriate comparator therapy:	
Therapy according to doctor's instructions[a]	
Lapatinib in combination with capecitabine	
Lapatinib	€ 40,210.23
Capecitabine	€ 2,449.36
Total:	€ 42,659.58
Lapatinib in combination with trastuzumab (only for patients with hormone-receptor negative breast cancer)	
Lapatinib	€ 32,168.18
Trastuzumab	€ 38,323.86
Total:	€ 70,492.04
Tucatinib in combination with capecitabine and trastuzumab	
Tucatinib	€ 79,683.50
Capectiabine	€ 2,449.36
Trastuzumab	€ 36,540.52
Total:	€ 118,673.38
[a] Only costs for lapatinib in combination with capecitabine, lapatinib in combination with trastuzumab and tucatinib in combination with capecitabine and trastuzumab are shown. In addition, trastuzumab in combination with cepacitabine represents a suitable comparator for the present benefit assessment in the context of therapy according to doctor's instructions. However, this medicinal treatment is 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 January 2023

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
Trastuzumab deruxtecan	Surcharge for production of parenteral solutions	€ 100	1	17.4	€ 1,740
Trastuzumab (in combination with tucatinib and capecitabine)	Surcharge for production of parenteral solutions	€ 100	1	17.4	€ 1,740
Trastuzumab (in combination with lapatinib)	Surcharge for production of parenteral solutions	€ 100	1	52.2	€ 5,220

5. 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 Trastuzumab deruxtecan

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which, on the basis of the marketing authorisation under Medicinal Products Act, can be used in a combination therapy with trastuzumab deruxtecan for the treatment of adults with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens:

<u>Adult patients with HER2-positive unresectable or metastatic breast cancer previously treated with two or more anti-HER2 based therapies</u>

- 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 2 February 2023.

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

Berlin, 2 February 2023

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

Prof. Hecken