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 (New Therapeutic Indication: Breast Cancer, HER2-low, Unresectable or Metastatic, Pretreated)

of 20 July 2023

At its session on 20 July 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. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Trastuzumab Deruxtecan in accordance with the resolution of 20 July 2023 on the therapeutic indication: "as monotherapy for the treatment of adult patients with advanced HER2-positive gastric or gastro-oesophageal junction (GOJ) adenocarcinoma who have received a prior trastuzumab-based therapeutic regimen":**

Trastuzumab deruxtecan

Resolution of: 20 July 2023
Entry into force on: 20 July 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 23 January 2023):

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

Therapeutic indication of the resolution (resolution of 20 July 2023):

See new therapeutic indication according to marketing authorisation.

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

Adults with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

Appropriate comparator therapy:

– Capecitabine

or

– Eribulin

or

– Vinorelbine

or

– an anthracycline or taxane-containing therapy (only for patients who have not yet received anthracycline and/or taxane-containing therapy or who are eligible for renewed anthracycline or taxane-containing treatment).

Extent and probability of the additional benefit of trastuzumab deruxtecan over capecitabine, eribulin, paclitaxel or nab-paclitaxel:

Indication of a considerable additional benefit

Study results according to endpoints: [1]

Adults with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	↔	Advantages in pain and insomnia; disadvantages in nausea and vomiting and diarrhoea; overall, no predominant advantage or disadvantage.
Health-related quality of life	↑	Advantages in physical functioning, cognitive functioning, social functioning and body image.
Side effects	↑↑	Disadvantage in the endpoints of SAEs and severe AEs (CTCAE grade ≥ 3) and in detail, advantages and disadvantages in the 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
∅: No data available.
n.a.: not assessable

DESTINY-Breast04 study
Study design: randomised, open-label, two-armed
Comparison: Trastuzumab deruxtecan **vs** therapy according to doctor's instructions (capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel)
Relevant sub-population: Treatment with capecitabine, eribulin, paclitaxel or nab-paclitaxel (gemcitabine excluded)
Data cut-off: 11 January 2022

[1] Data from the dossier assessment of the IQWiG (A23-07) and from the addendum (A23-52), unless otherwise indicated.

Mortality

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions[a]		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)[b]
Overall survival					
	344	23.4 [20.0; n.c.] 137 (39.8)	165	17.0 [15.1; 20.2] 78 (47.3)	0.64 [0.48; 0.85] 0.002 + 6.4 months
Effect modification by the characteristic "visceral disease"					
yes	306	21.7 [19.5; 24.7] 130 (42.5)	143	17.1 [15.2; 22.4] 65 (45.5)	0.73 [0.54; 0.99] 0.039 + 4.6 months
no	38	n.a. 7 (18.4)	22	15.1 [12.6; 20.6] 13 (59.1)	0.22 [0.09; 0.57] 0.001
					Interaction: 0.018

Morbidity

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions[a]		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)[b]
Progression-free survival (PFS)[c]					
	344	9.8 [8.5; 11.3] 229 (66.6)	165	5.3 [4.3; 6.9] 114 (69.1)	0.53 [0.42; 0.67] < 0.0001 + 4.5 months
Disease symptomatology					
Symptom scales of the EORTC QLQ-C30 (time to first deterioration)[d]					
Fatigue	344	4.2 [2.8; 5.5] 220 (64.0)	165	2.8 [1.4; 3.3] 100 (60.6)	0.81 [0.63; 1.03] 0.081
Nausea and vomiting	344	1.4 [1.4; 1.6]	165	8.2 [6.0; 9.8]	2.12 [1.61; 2.78]

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions[a]		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)[b]
		239 (69.5)		68 (41.2)	< 0.001 - 6.8 months
Pain	344	8.5 [5.9; 10.6] 177 (51.5)	165	4.4 [2.8; 7.2] 86 (52.1)	0.69 [0.53; 0.898] 0.005 + 4.1 months
Dyspnoea	344	13.2 [8.3; 21.7] 148 (43.0)	165	6.8 [5.1; n.c.] 66 (40.0)	0.80 [0.60; 1.08] 0.148
Insomnia	344	16.0 [11.1; n.c.] 137 (39.8)	165	5.4 [4.2; 7.1] 76 (46.1)	0.56 [0.42; 0.74] < 0.001 + 10.6 months
Appetite loss	344	5.1 [3.2; 6.9] 197 (57.3)	165	7.0 [4.6; 9.8] 74 (44.8)	1.20 [0.92; 1.58] 0.190
Constipation	344	4.2 [2.9; 5.6] 205 (59.6)	165	5.9 [4.5; 8.4] 73 (44.2)	1.17 [0.89; 1.54] 0.255
Diarrhoea	344	9.4 [7.0; 15.3] 163 (47.4)	165	13.3 [9.0; n.c.] 54 (32.7)	1.37 [1.003; 1.87] 0.049 - 3.9 months
Symptom scales of the EORTC QLQ-BR23 (time to first deterioration)[d]					
Side effects of systemic therapy	344	4.2 [2.8; 5.9] 193 (56.1)	165	2.8 [1.5; 4.5] 92 (55.8)	0.82 [0.64; 1.06] 0.131
Chest symptoms	344	n.a. [20.3; n.c.] 93 (27.0)	165	n.a. 37 (22.4)	0.89 [0.60; 1.31] 0.554
Arm symptoms	344	7.7 [6.7; 11.2] 166 (48.3)	165	5.1 [2.9; n.c.] 73 (44.2)	0.78 [0.59; 1.03] 0.079
Burden due to hair loss	No suitable data[e]				
Health status (time to first deterioration)[f]					
EQ-5D VAS					

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions[a]		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)[b]
	344	16.4 [11.1; n.c.] 132 (38.4)	165	8.4 [5.4; n.c.] 55 (33.3)	0.82 [0.59; 1.13] 0.220

Health-related quality of life

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions[a]		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)[b]
Health-related quality of life					
Functional scales of the EORTC QLQ-C30 (time to first deterioration)[g]					
Global health status	344	5.6 [4.2; 7.9] 190 (55.2)	165	4.0 [2.8; 5.9] 90 (54.5)	0.81 [0.63; 1.04] 0.097
Physical functioning	344	8.7 [7.1; 11.3] 169 (49.1)	165	4.5 [3.0; 5.8] 87 (52.7)	0.62 [0.47; 0.81] < 0.001 + 4.2 months
Role functioning	344	4.2 [2.9; 5.9] 198 (57.6)	165	3.2 [1.6; 4.4] 93 (56.4)	0.81 [0.63; 1.04] 0.089
Emotional functioning	344	10.4 [8.3; 13.1] 161 (46.8)	165	7.1 [5.7; 11.7] 64 (38.8)	0.89 [0.66; 1.20] 0.432
Cognitive functioning	344	6.5 [5.0; 7.7] 187 (54.4)	165	4.2 [3.1; 6.3] 90 (54.5)	0.75 [0.58; 0.97] 0.028 + 2.3 months
Social functioning	344	5.9 [4.2; 9.7] 194 (56.4)	165	3.4 [2.1; 4.7] 96 (58.2)	0.73 [0.57; 0.94] 0.014 + 2.5 months
Functional scales of the EORTC QLQ-BR23 (time to first deterioration)[g]					
Body image	344	12.8	165	5.1	0.67

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions[a]		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)[b]
		[9.6; n.c.] 143 (41.6)		[2.9; 16.9] 75 (45.5)	[0.51; 0.897] 0.006 + 7.7 months
Sexual functioning	344	n.a. 73 (21.2)	165	n.a. 31 (18.8)	0.91 [0.59; 1.39] 0.651
Sex pleasure	No suitable data[e]				
Future prospects	344	16.9 [14.1; n.c.] 123 (35.8)	165	n.a. [11.1; n.c.] 49 (29.7)	0.98 [0.70; 1.38] 0.916

Side effects

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions[a]		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)[b]
Adverse events (AEs) (presented additionally)					
	343	0.1 [n.c.; n.c.] 341 (99.4)	156	0.1 [0.1; 0.1] 153 (98.1)	-
Serious adverse events (SAE)					
	343	n.a. [24.4; n.c.] 97 (28.3)	156	n.a. [9.2; n.c.] 41 (26.3)	0.66 [0.45; 0.97] 0.034
Severe adverse events (CTCAE grade ≥ 3)					
	343	7.2 [5.0; 10.5] 184 (53.6)	156	0.9 [0.5; 2.0] 103 (66.0)	0.50 [0.39; 0.64] < 0.001 + 6.3 months
Discontinuation due to AEs					
	343	n.a. [24.4; n.c.] 56 (16.3)	156	n.a. [16.2; n.c.] 13 (8.3)	1.09 [0.58; 2.04] 0.784

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions[a]		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)[b]
Specific adverse events					
Hand-foot syndrome (PT, AE)	343	n.a. 4 (1.2)	156	n.a. 24 (15.4)	0.05 [0.02; 0.15] < 0.001
Cardiac disorders (SOC, severe AE)	343	n.d.	156	n.d.	n.d.
Thrombocytopenia (PT, severe AEs)	343	n.a. 19 (5.5)	156	n.a. 0 (0)	n.a. 0.009
Gastrointestinal disorders (SOC, severe AE)	343	0.1 [0.1; 0.1] 302 (88.0)	156	0.7 [0.5; 1.5] 106 (67.9)	2.13 [1.69; 2.68] < 0.001 - 0.6 months
Infections and infestations (SOC, SAE)	343	n.a. 28 (8.2)	156	n.a. 2 (1.3)	4.22 [0.99; 17.92] 0.034
Neutropoenia (PT, severe AE)	343	n.a. 20 (5.8)	156	n.a. 23 (14.7)	0.32 [0.17; 0.59] < 0.001
Nausea (PT, severe AEs)	343	n.a. 16 (4.7)	156	n.a. 0 (0)	n.a. 0.010

[a] Capecitabine or eribulin or paclitaxel or nab-paclitaxel
[b] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation
[c] Data from: Written statement by the pharmaceutical company dated 23 May 2023
[d] An increase in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[e] Unclear percentage of patients with missing values at the start and during the course of the study.
[f] A decrease in score by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[g] A decrease in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).

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; 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-BR23 = Quality of Life Questionaire – Breast Cancer 23; QLQ-C30 = Quality of Life Questionnaire – Core 30; SOC = system organ class; VAS = visual analogue scale; vs = versus

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

Adults with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

approx. 1,350 – 4,700 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: 27 April 2023):

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 who are experienced in the treatment of patients with breast cancer, as well as specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement.

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:

The annual treatment costs shown refer to the first year of treatment.

Adults with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Trastuzumab deruxtecan	€ 151,298.57
Appropriate comparator therapy:	
Capecitabine monotherapy	
Capecitabine	€ 2,450.29
Eribulin monotherapy	
Eribulin	€ 63,674.43

Designation of the therapy	Annual treatment costs/ patient
Vinorelbine monotherapy	
Vinorelbine	€ 7,061.95 - € 8,513.24
Taxanes	
Docetaxel	€ 15,410.83
nab-paclitaxel	€ 35,451.63
Paclitaxel	
Paclitaxel	€ 15,554.90
Additionally required SHI services	€ 241.99
Total	€ 16,155.33
Anthracyclines	
Doxorubicin	€ 2,081.60 - € 3,121.25
Liposomal pegylated doxorubicin	€ 36,547.29
Epirubicin	€ 4,677.70 - € 5,139.20

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 July 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
Medicinal product to be assessed:					
Trastuzumab deruxtecan	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
Appropriate comparator therapy:					
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Doxorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	5 - 11	€ 500 - € 1,100
Pegylated liposomal doxorubicin	Surcharge for production of a parenteral	€ 100	1	13.0	€ 1,300

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	preparation containing cytostatic agents				
Epirubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	10 - 16	€ 1,000 - € 1,600
Eribulin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	34.8	€ 3,480
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1740
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	52.1	€ 5,210

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 adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or in whom a relapse has occurred during or within 6 months after completed adjuvant chemotherapy:

Adults with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

– 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 20 July 2023.

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

Berlin, 20 July 2023

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

Prof. Hecken