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, HR+, HER2-low or HER2-ultralow, after at least 1 endocrine therapy)

of 16 October 2025

At their session on 16 October 2025, 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. 5 to the information on the benefit assessment of Trastuzumab deruxtecan in accordance with the resolution of 16 May 2024:

Trastuzumab deruxtecan

Resolution of: 16 October 2025
Entry into force on: 16 October 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 31 March 2025):

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment.

Therapeutic indication of the resolution (resolution of 16 October 2025):

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 hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment

Appropriate comparator therapy:

- Doxorubicin

or

- liposomal doxorubicin (only suitable for female patients)

or

- epirubicin

or

- docetaxel (only suitable for female patients)

or

- paclitaxel (only suitable for female patients who are not eligible for anthracycline-containing systemic therapy)

or

- nab-paclitaxel (only suitable for female patients who are not eligible for anthracycline-containing systemic therapy)

or

- capecitabine (only suitable for patients who have failed anthracycline and taxane-containing therapy or who are not eligible for further anthracycline treatment)

or

- vinorelbine (only suitable for patients who are not eligible for anthracycline or taxane-containing systemic therapy)

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

Hint for a minor additional benefit

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	↑	Advantage in health status (PGIC endpoint).
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↔	No relevant differences 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
∅: No data available.
n.a.: not assessable

DESTINY-Breast06 study: Trastuzumab deruxtecan versus chemotherapy according to the doctor's instructions (capecitabine, paclitaxel or nab-paclitaxel)

Mortality

Endpoint	Trastuzumab deruxtecan		Therapy according to doctor's instructions		Intervention versus 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 Absolute difference (AD)[a]
Mortality					
	436	30.5 [28.4; 33.3] *232 (53.2)*	430	27.2 [24.7; 29.2] *253 (58.8)*	0.79 [0.66; 0.94]; 0.008[b] AD = 3.3 months
Effect modification by the "age" characteristic					
< 65 years	302	32.7 [29.9; 36.1] *149 (49.3)*	297	27.1 [24.2; 29.2] *178 (59.9)*	0.70 [0.56; 0.87]; 0.001
≥ 65 years	134	26.4 [21.2; 31.6] *83 (61.9)*	133	27.9 [21.9; 36.9] *75 (56.4)*	1.03 [0.76; 1.42]; 0.835
					Interaction: 0.047

Morbidity

Progression-free survival (PFS)[c]					
	436	13.2 [12.0; 15.2] *272 (62.4)*	430	8.1 [7.0; 9.0] *271 (63.0)*	0.64 [0.54; 0.76]; < 0.0001
Symptomatology					
EORTC QLQ-C30, EORTC QLQ-BR45, PGIS					
	No suitable data				
Health status					
EQ-5D VAS					
	No suitable data				
PGIC (time to 1st deterioration)[d]					
	436	24.3 [16.5; n.c.] *158 (36.2)*	430	8.9 [7.0; 12.5] *177 (41.2)*	0.60 [0.49; 0.751]; < 0.001[e] AD = 15.4 months

Health-related quality of life

EORTC QLQ-C30, EORTC QLQ-BR45	
	No suitable data

Side effects

Endpoint	**Trastuzumab deruxtecan**		**Therapy according to doctor's instructions**		Intervention versus 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 Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	434	0.1 [0.1; 0.1] *429 (98.8)*	417	0.3 [0.2; 0.3] *397 (95.2)*	-
Serious adverse events (SAE)					
	434	n.r. *90 (20.7)*	417	n.r. *67 (16.1)*	0.97 [0.70; 1.34]; 0.851
Severe adverse events (CTCAE grade 3 or 4)					
	434	9.0 [5.7; 12.0] *239 (55.1)*	417	11.0 [6.2; n.c.] *186 (44.6)*	1.05 [0.87; 1.27]; 0.626[e]

Therapy discontinuation due to adverse events					
	434	n.r. [33.9; n.c.] *71 (16.4)*	417	n.r. *41 (9.8)*	1.16 [0.79; 1.73]; 0.458[e]
Specific adverse events					
Cardiac disorders (SOC, severe AEs)	434	n.d. *2 (0.5)*	417	n.d. *6 (1.4)*	n.d.
Thrombocytopenia (PT, severe AEs)	434	n.r. *18 (4.1)*	417	n.r. *0 (0)*	n.c.; < 0.001[f]
ILD/ pneumonitis (AEs)	434	n.r. *59 (13.6)*	417	n.r. *1 (0.2)*	37.80 [8.31; 668.37] < 0.001[g]
Hand-foot syndrome (PT, AEs)	434	n.r. *5 (1.2)*	417	n.r. [12.5; n.c.] *146 (35.0)*	0.02 [0.01; 0.05] < 0.001[e]
Respiratory, thoracic and mediastinal disorders (SOC, AEs)	434	12.2 [9.9; 15.3] *221 (50.9)*	417	n.r. [20.4; n.c.] *109 (26.1)*	1.58 [1.26; 1.99]; < 0.001[e]
Loss of appetite (PT, AEs)	434	n.r. *114 (26.3)*	417	39.4 [n.c.] *51 (12.2)*	2.11 [1.53; 2.97]; < 0.001[e]
Constipation (PT, AEs)	434	n.r. *139 (32.0)*	417	n.r. *62 (14.9)*	2.10 [1.56; 2.85]; < 0.001[e]
Nausea (PT, AEs)	434	0.2 [0.1; 0.3] *307 (70.7)*	417	n.r. [23.2; n.c.] *128 (30.7)*	3.37 [2.75; 4.16]; < 0.001[e]
Vomiting (PT, AEs)	434	n.r. *154 (35.5)*	417	n.r. *50 (12.0)*	3.09 [2.26; 4.30]; < 0.001[e]
Alopecia (PT, AEs)	434	8.5 [3.7; n.c.] *212 (48.8)*	417	n.r. *88 (21.1)*	2.51 [1.97; 3.24]; < 0.001[e]
Oedema, peripheral (PT, AEs)	434	n.r. *40 (9.2)*	417	n.r. [29.5; n.c.] *61 (14.6)*	0.46 [0.30; 0.68]; < 0.001[e]
Investigations (SOC, severe AEs)	434	n.r. *104 (24.0)*	417	n.r. *47 (11.3)*	1.89 [1.35; 2.70]; < 0.001[e]
Musculoskeletal and connective tissue disorders (SOC, severe AEs)	434	n.r. *5 (1.2)*	417	n.r. *10 (2.4)*	0.32 [0.10; 0.91]; 0.040[e]
Nervous system disorders (SOC, severe AEs)	434	n.r. *9 (2.1)*	417	n.r. *18 (4.3)*	0.34 [0.14; 0.75]; 0.009[e]
Anaemia (PT, severe AEs)	434	n.r. [40.3; n.c.] *43 (9.9)*	417	n.r. *18 (4.3)*	1.89 [1.10; 3.37]; 0.025[e]

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Effect, CI and p value: Cox proportional hazards model, stratified by prior use of CDK-4/6 inhibitors (yes vs no) and HER2 IHC expression (IHC > 0 and < 1+ vs IHC 1+ vs IHC 2+/ISH-). CI and p value: Profile likelihood method based on this Cox model.
[c] Information provided by the pharmaceutical company in the written statement
[d] An assessment by the patients as "minimally worse", "moderately worse" and "much worse" compared to the start of the study is considered as clinically relevant deterioration.
[e] Effect, CI and p value: Cox proportional hazards model, unstratified. CI and p value: Profile likelihood method based on this Cox model.
[f] Effect, profile likelihood CI and profile likelihood p value based on an (unstratified) Cox proportional hazards model cannot be estimated here according to the pharmaceutical company. The p value given here is therefore derived from an unstratified log-rank test.
[g] Effect, CI and p value: Cox proportional hazards model, presumably unstratified. CI and p value: Profile likelihood method based on this Cox model.

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; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with (at least 1) event; N = number of patients evaluated; n.c. = not calculable; n.r. = not reached; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PT = preferred term; QLQ-BR45 = Quality of Life Questionnaire – Breast Cancer 45; QLQ-C30 = Quality of Life Questionnaire – Core 30; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale

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

Adults with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment

Approx. 1,615 to 6,200 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: 25 June 2025):

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 from other specialist groups participating in the Oncology Agreement.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency EMA 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:

Adults with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Trastuzumab deruxtecan	€ 99,648.41
Appropriate comparator therapy:	
Anthracycline or taxane-containing systemic therapy	
Doxorubicin	
Doxorubicin	€ 1,868.45 – € 2,740.39
Liposomal doxorubicin (only suitable for female patients)	
Doxorubicin PEG-liposomal	€ 36,557.82
Epirubicin	
Epirubicin	€ 4,685.70 – € 5,154.27
Docetaxel (only suitable for female patients)	
Docetaxel	€ 15,420.05
Paclitaxel (only suitable for female patients who are not eligible for anthracycline-containing systemic therapy)	
Paclitaxel	€ 15,545.68
Additionally required SHI services	€ 271.07
nab-paclitaxel (only suitable for female patients who are not eligible for anthracycline-containing systemic therapy)	
nab-paclitaxel	€ 35,474.25
Capecitabine (only suitable for patients who are not eligible for anthracycline or taxane-containing systemic therapy)	
Capecitabine	€ 2,455.61
Vinorelbine (only suitable for patients who are not eligible for anthracycline or taxane-containing systemic therapy)	
Vinorelbine	€ 7,510.74 – € 9,376.96

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2025)

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 with trastuzumab deruxtecan	€ 100	1	17.4	€ 1,740
Appropriate comparator therapy					
Doxorubicin	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	1	5 - 11	€ 500 – € 1,100
Doxorubicin PEG-liposomal	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	1	13.0	€ 1,300
Epirubicin	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	1	10 – 16	€ 1,000 – € 1,600
Docetaxel	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	1	17.4	€ 1,740
Paclitaxel	Surcharge for the preparation of a parenteral solution containing cytostatic agents	€ 100	1	17.4	€ 1,740
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. 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:

Adults with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment

- 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 16 October 2025.

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

Berlin, 16 October 2025

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

Prof. Hecken