Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Trastuzumab Emtansine (New Therapeutic Indication: Adjuvant Treatment of Early Breast Cancer)

of 2 July 2020

On 2 July 2020, the Federal Joint Committee (G-BA) resolved by written statement to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD 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 emtansine in accordance with the resolution of 19 June 2014:

Trastuzumab emtansine

Resolution of: 2 July 2020
Entry into force on: 2 July 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 18 December 2019):

Trastuzumab emtansine (Kadcyla®), as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

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

Adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy

Appropriate comparator therapy:

Continuation of anti-HER2 directed therapy with trastuzumab initiated preoperatively

Extent and probability of the additional benefit of trastuzumab emtansine compared with trastuzumab:

Indication of a minor additional benefit

Study results according to endpoints:[1]

Adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy

[1] Data from the dossier assessment of the IQWiG (A20-07) unless otherwise indicated.

KATHERINE study: Trastuzumab emtansine vs trastuzumab

Study design: RCT, open, parallel

Mortality

Endpoint	**Trastuzumab emtansine**		**Trastuzumab**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI]; p value
Overall survival					
	743	n.a. [n.c.; n.c.] *42 (5.7)*	743	n.a. [n.c.; n.c.] *56 (7.5)*	HR[b]: 0.70 [0.47; 1.05]; 0.085

Morbidity

Endpoint	**Trastuzumab emtansine**		**Trastuzumab**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI]; p value Absolute difference (AD)[a]
Relapses					
Relapses (total)	743	*98 (13.2)*	743	*167 (22.5)*	RR: 0.59 [0.47; 0.74]; < 0.001 AD: 9.3%
Events included in the combined endpoint relapses					
Ipsilateral invasive local breast cancer recurrence	743	*6 (0.8)*	743	*30 (4.0)*	—[c]
Ipsilateral invasive regional breast cancer recurrence	743	*5 (0.7)*	743	*11 (1.5)*	—[c]
Distant recurrence	743	*75 (10.1)*	743	*108 (14.5)*	—[c]
Contralateral invasive breast cancer	743	*3 (0.4)*	743	*10 (1.3)*	—[c]
Secondary primary carcinoma (not breast cancer)	743	*4 (0.5)*	743	*4 (0.5)*	—[c]

DCIS (ipsilateral or contralateral)	743	*3 (0.4)*	743	*1 (0.1)*	—[c]
Death from any cause	743	*2 (0.3)*	743	*3 (0.4)*	—[c]
Disease-free survival (DFS)[d)]					
	743	n.a. [n.c.; n.c.] *98 (13.2)*	743	n.a. [n.c.; n.c.] *167 (22.5)*	HR[b]: 0.53 [0.41; 0.68]; < 0.001 AD: 9.3%

Endpoint	**Trastuzumab emtansine**		**Trastuzumab**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI]; p value Absolute difference (AD)[a]
Symptomatology					
EORTC QLQ-C30 symptom scales – patients with deterioration of ≥ 10 points at the end of therapy					
Fatigue	534	211 (39.5)	536	175 (32.6)	1.21 [1.03; 1.42]; 0.020 AD: 7%
Nausea and vomiting	534	89 (16.7)	536	63 (11.8)	1.42 [1.05; 1.91]; 0.022 AD: 4.9%
Pain	534	177 (33.1)	536	146 (27.2)	1.22 [1.01; 1.46]; 0.036 AD: 5.9%
Dyspnoea	534	111 (20.8)	536	111 (20.7)	1.00 [0.79; 1.27]; 0.975
Insomnia	534	140 (26.2)	536	142 (26.5)	0.99 [0.81; 1.21]; 0.919
Loss of appetite	534	101 (18.9)	536	58 (10.8)	1.75 [1.30; 2.36]; < 0.001 AD: 8.1%
Constipation	534	159 (29.8)	536	97 (18.1)	1.65 [1.32; 2.05]; < 0.001 AD: 11.7%
Diarrhoea	534	40 (7.5)	536	56 (10.5)	0.72

					[0.49; 1.05]; 0.091
EORTC QLQ-BR23 symptom scales – patients with deterioration of ≥ 10 points at the end of therapy					
Side effects of the systemic therapy	534	144 (27.0)	534	94 (17.6)	1.53 [1.22; 1.93]; < 0.001 AD: 9.4%
Symptoms in the chest area	534	99 (18.5)	534	88 (16.5)	1.12 [0.87; 1.46]; 0.376
Symptoms in the arm area	534	190 (35.6)	534	150 (28.1)	1.27 [1.06; 1.51]; 0.009 AD: 7.5%
Burden of hair loss	No usable data				

Endpoint	**Trastuzumab emtansine**			**Trastuzumab**			Intervention vs control
	N	Values at start of study MV (SE)	Change MV (SE)	N	Values at start of study MV (SE)	Change MV (SE)	MD [95% CI]; p value
Symptomatology *(EORTC QLQ-C30 symptom scales [f]) – 12-month follow-up*							
Fatigue	640	no data available	2.48 (0.63)	612	no data availa-ble	0.76 (0.64)	1.73 [-0.03; 3.48]; no data availa-ble
Nausea and vomit-ing	640	no data available	1.94 (0.29)	612	no data availa-ble	1.18 (0.30)	0.75 [-0.06; 1.57]; no data availa-ble
Pain	640	no data available	1.06 (0.66)	612	no data availa-ble	-0.09 (0.68)	1.15 [-0.71; 3.01]; no data availa-ble
Dyspnoea	640	no data available	3.32 (0.60)	612	no data availa-ble	3.65 (0.62)	-0.33 [-2.03; 1.37]; no data availa-ble
Insomnia	640	no data available	0.45 (0.84)	612	no data availa-ble	1.59 (0.86)	-1.14 [-3.50; 1.22]; no data availa-ble
Loss of appetite	640	no data available	1.93 (0.48)	612	no data availa-ble	0.08 (0.49)	1.85 [0.50; 3.20];

							no data available Hedges' g: 0.15 [0.04; 0.26]
Constipation	640	no data available	5.54 (0.62)	612	no data available	2.89 (0.64)	2.65 [0.90; 4.39]; no data available Hedges' g: 0.17 [0.06; 0.28]
Diarrhoea	640	no data available	-2.62 (0.40)	612	no data available	-0.95 (0.41)	-1.67 [-2.78; -0.55]; no data available Hedges' g: -0.17 [-0.28; -0.05]
Symptomatology *(EORTC QLQ-BR23 symptom scales [f]) – 12-month follow-up*							
Side effects of the systemic therapy	638	no data available	3.39 (0.42)	610	no data available	1.21 (0.43)	2.18 [1.01; 3.35]; no data available Hedges' g: 0.21 [0.10; 0.32]
Symptoms in the chest area	638	no data available	-2.51 (0.50)	610	no data available	-3.93 (0.52)	1.43 [0.01; 2.84]; no data available Hedges' g: 0.11 [0.00; 0.22]
Symptoms in the arm area	638	no data available	-1.40 (0.60)	610	no data available	-3.19 (0.62)	1.80 [0.10; 3.50]; no data available Hedges' g: 0.12 [0.01; 0.23]
Burden of hair loss	No usable data						

Endpoint	**Trastuzumab emtansine**			**Trastuzumab**			Intervention vs control
	N	Values at start of study MV (SE)	Change MV (SE)	N	Values at start of study MV (SE)	Change MV (SE)	MD [95% CI]; p value

Health status (EQ-5D VAS [e])							
12-month follow-up	618	no data available	0.38 (0.47)	600	no data availa-ble	1.95 (0.48)	-1.57 [-2.89; -0.24]; no data available Hedges' g: -0.13 [-0.25; -0.02]

Endpoint	**Trastuzumab emtansine**		**Trastuzumab**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI]; p value
Health status (EQ-5D VAS) *(deterioration of ≥ 10 points)*					
End of therapy	526	118 (22.4)	532	97 (18.2)	1.23 [0.97; 1.56] 0.091
12-month follow-up	No usable data				

Health-related quality of life

Endpoint	**Trastuzumab emtansine**		**Trastuzumab**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI]; p value Absolute difference (AD)[a]
EORTC QLQ-C30 functional scales – patients with deterioration of ≥ 10 points at the end of therapy					
Global health status	534	123 (23.0)	535	112 (20.9)	1.10 [0.88; 1.38]; 0.408
Physical functioning	534	120 (22.5)	536	91 (17.0)	1.32 [1.04; 1.69]; 0.025 AD: 5.5%
Role functioning	534	141 (26.4)	536	122 (22.8)	1.16 [0.94; 1.43]; 0.167
Emotional function-ing	534	208 (39.0)	535	198 (37.0)	1.05 [0.90; 1.23]; 0.513
Cognitive function-ing	534	201 (37.6)	535	190 (35.5)	1.06 [0.90; 1.24]; 0.471
Social functioning	534	131 (24.5)	535	102 (19.1)	1.29 [1.02; 1.62]; 0.031

					AD: 5.4%
EORTC QLQ-BR23 functional scales – patients with deterioration of ≥ 10 points at the end of therapy					
Body image	534	91 (17.0)	534	106 (19.9)	0.86 [0.67; 1.11]; 0.237
Sexual functioning	No usable data				
Sexual enjoyment	No usable data				
Future perspective	534	106 (19.9)	534	91 (17.0)	1.16 [0.90; 1.50]; 0.237

Endpoint	**Trastuzumab emtansine**			**Trastuzumab**			Intervention vs control
	N	Values at start of study MV (SE)	Change MV (SE)	N	Values at start of study MV (SE)	Change MV (SE)	MD [95% CI]; p value
EORTC QLQ-C30 functional scales [f] – 12-month follow-up							
Global health status	640	no data available	0.23 (0.51)	612	no data availa-ble	1.63 (0.52)	-1.40 [-2.84; 0.04]; no data availa-ble
Physical functioning	640	no data available	-0.31 (0.43)	612	no data availa-ble	1.32 (0.44)	-1.64 [-2.84; -0.44]; no data availa-ble Hedges' g: -0.15 [-0.26; -0.04]
Role functioning	640	no data available	2.00 (0.67)	612	no data availa-ble	4.20 (0.69)	-2.21 [-4.09; -0.33]; no data availa-ble Hedges' g: -0.13 [-0.24; -0.02]
Emotional function-ing	640	no data available	-1.27 (0.64)	612	no data availa-ble	-2.07 (0.65)	0.80 [-0.99; 2.59]; no data available
Cognitive function-ing	640	no data available	-5.67 (0.64)	612	no data availa-ble	-5.10 (0.65)	-0.57 [-2.36; 1.22]; no data available
Social functioning	640	no data available	3.83 (0.64)	612	no data availa-ble	6.21 (0.65)	-2.38 [-4.17; -0.59]; no data availa-ble Hedges' g:

							-0.15 [-0.26; -0.04]
EORTC QLQ-BR23 functional scales [f] – 12-month follow-up							
Body image	638	no data available	5.97 (0.71)	610	no data availa-ble	3.60 (0.72)	2.38 [0.39; 4.36]; no data available Hedges' g: 0.13 [0.02; 0.24]
Sexual functioning	538	no data available	3.57 (0.69)	517	no data availa-ble	3.95 (0.71)	-0.38 [-2.32; 1.57]; no data available
Sexual enjoyment	216	no data available	1.00 (1.32)	218	no data availa-ble	3.05 (1.41)	-2.05 [-5.84; 1.74]; no data available
Future perspective	638	no data available	6.43 (0.81)	610	no data availa-ble	6.45 (0.83)	-0.03 [-2.29; 2.24]; no data available

Side effects

Endpoint	**Trastuzumab emtansine**		**Trastuzumab**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value Absolute difference (AD)[a]
Adverse events (presented additionally)					
	740	731 (98.8)	720	672 (93.3)	–
Serious adverse events (SAEs)					
	740	94 (12.7)	720	58 (8.1)	1.58 [1.16; 2.15]; 0.004 AD: 4.6%
Severe adverse events (CTCAE grade 3 or 4)					
	740	190 (25.7)	720	111 (15.4)	1.67 [1.35; 2.06]; < 0.001 AD: 10.3%
Therapy discontinuation due to adverse events					
	740	133 (18.0)	720	15 (2.1)	8.63 [5.11; 14.57]; < 0.001 AD: 15.9%
Specific adverse events					
Cardiac disorders (SOC, severe AEs	740	2 (0.3)	720	7 (1.0)	0,28 [0,06; 1,33];

(CTCAE grade ≥ 3))					< 0,088 AD: 0,7%
Platelet count decreased (PT, severe AEs [CTCAE grade ≥ 3])	740	42 (5.7)	720	2 (0.3)	20,43 [4,96; 84,09]; < 0,001 AD: 5,4%
Fatigue (PT, AE)	740	366 (49.5)	720	243 (33.8)	1,47 [1,29; 1,66]; < 0,001 AD: 15,7%
Fever (PT, AE)	740	77 (10.4)	720	29 (4.0)	2,58 [1,71; 3,91]; < 0,001 AD: 6,4%
Gastrointestinal disorders (SOC, severe AEs [CTCAE grade ≥ 3])	740	21 (2.8)	720	7 (1.0)	2,92 [1,25; 6,82]; 0,009 AD: 1,8%
Nausea (PT, AE)	740	308 (41.6)	720	94 (13.1)	3,19 [2,59; 3,92]; < 0,001 AD: 28,5%
Constipation (PT, AE)	740	126 (17.0)	720	59 (8.2)	2,08 [1,55; 2,78]; < 0,001 AD: 8,8%
Vomiting (PT, AE)	740	108 (14.6)	720	37 (5.1)	2,84 [1,98; 4,07]; < 0,001 AD: 9,5%
Dry mouth (PT, AE)	740	100 (13.5)	720	9 (1.3)	10,81 [5,51; 21,22]; < 0,001 AD: 12,2%
Stomatitis (PT, AE)	740	80 (10.8)	720	27 (3.8)	2,88 [1,89; 4,41]; < 0,001 AD: 7%
Headache (PT, AE)	740	210 (28.4)	720	122 (16.9)	1,67 [1,37; 2,04]; < 0,001 AD: 11,5%
Peripheral sensory neuropathy (PT, severe AEs	740	10 (1.4)	720	0 (0)	20,43 [1,2; 348,05]; 0,002

[CTCAE grade ≥ 3])					AD: 1,4%
Infections and infestations (SOC, SAE)	740	37 (5.0)	720	21 (2.9)	1,71 [1,01; 2,9]; 0,042 AD: 2,1%
Respiratory, thoracic, and mediastinal disorders (SOC, AE)	740	329 (44.5)	720	219 (30.4)	1,46 [1,27; 1,68]; < 0,001 AD: 14,1%
Eye disorders (SOC, AE)	740	133 (18.0)	720	63 (8.8)	2,05 [1,55; 2,72]; < 0,001 AD: 9,2%

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Unstratified Cox model, p value: Two-sided log-rank test
[c] No presentation of effect estimates. The events shown do not fully represent the endpoint.
[d] Includes the same components as the relapse endpoint
[e.] A positive change from start of study to the assessment point in question indicates an improvement; a positive effect estimate indicates an advantage for the intervention.
[f.] A positive change from start of study to the assessment point in question indicates a deterioration of symptomatology; a negative effect estimate indicates an advantage for the intervention.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; HR = hazard ratio; CI = confidence interval; MD = mean difference; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; RR = relative risk; SOC = System Organ Class; PT = Preferred Term; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment, no final data.
Morbidity	↑↑	Benefits in preventing recurrences, detriments in symptom scales.
Health-related quality of life	↓	Detriments for functional scales.
Side effects	↓↓	Detriments in the endpoints serious adverse events (SAEs), severe AEs (CTCAE-grade ≥ 3) and therapy discontinuation due to AEs and in detail 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

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

Adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy

approx. 1,980 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 Kadcyla® (active ingredient: trastuzumab emtansine) at the following publicly accessible link (last access: 10 March 2020):

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

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

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on trastuzumab emtansine:

- Information for healthcare professionals

4. Treatment costs

Annual treatment costs:

Adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Trastuzumab emtansine	€ 69,537.44
Appropriate comparator therapy:	
Trastuzumab	€ 35,769.98

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Trastuzumab emtansine	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	14	€ 994
Trastuzumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	17.4	€ 1,235

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 2 July 2020.**
2. **The period of validity of the resolution is limited to 30 September 2024.**

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

Berlin, 2 July 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken