Gemeinsamer Bundesausschuss

Resolution

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-L):

Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V:

Pertuzumab/trastuzumab (breast cancer, HER2-positive, early stage at high risk of recurrence, adjuvant)

of 15 July 2021

At its session on 15 July 2021, 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 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 pertuzumab/trastuzumab in accordance with the resolution of 15 July 2021:

Pertuzumab/trastuzumab

Resolution of: 15 July 2021
Entry into force on: 15 July 2021
BAnz AT TT. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 21 December 2020):

Phesgo is indicated for use in combination with chemotherapy for adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.

Therapeutic indication of the resolution (resolution of 15 July 2021):

see therapeutic indication according to marketing authorisation.

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

Adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.

Appropriate comparator therapy for pertuzumab/trastuzumab in combination with chemotherapy:

a therapeutic regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if appropriate, an anthracycline (doxorubicin or epirubicin)

Extent and probability of the additional benefit of pertuzumab/trastuzumab in combination with chemotherapy compared to trastuzumab in combination with chemotherapy:

Hint for a minor additional benefit.

Study results according to endpoints:[1]

Adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-11) unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment, no final data
Morbidity	↑	Advantages in the prevention of recurrences
Health-related quality of life	↔	No relevant difference for the benefit assessment
Side effects	↓	Disadvantages in the endpoints serious adverse events (SAE) and serious AEs (CTCAE grade ≥ 3)

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

APHINITY study: Pertuzumab + trastuzumab + chemotherapy **vs** placebo + trastuzumab + chemotherapy

Relevant sub-population: Adults with HER2-positive early stage breast cancer at high risk of recurrence according to the marketing authorisation, defined as nodal-positive or hormone receptor-negative disease (approximately 75% of the study population)

Mortality

Endpoint	Pertuzumab + trastuzumab + chemotherapy		Placebo + trastuzumab + chemotherapy		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 (%)*	RR [95% CI] p value
Overall survival (data cut-off: 19.06.2019)					
	1811	n. a. [n. c.; n. c.] *108 (6.0)*	1823	n. a. [n. c.; n. c.] *130 (7.1)*	HR[a]: 0.82 [0.64; 1.06] 0.136

Morbidity

Endpoint	Pertuzumab + trastuzumab + chemotherapy		Placebo + trastuzumab + chemotherapy		Intervention vs Control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Recurrences (data cut-off: 19.06.2019)					
Recurrence rate	1811	219 (12.1)	1823	287 (15.7)	0.77 [0.65; 0.905] 0.002[b]
ipsilateral invasive local breast cancer¬recurrent	1811	14 (6.4)[d]	1823	32 (11.1)[d]	—
ipsilateral invasive regional breast cancer¬recurrent	1811	9 (4.1)[d]	1823	14 (4.9)[d]	—
remote recurrence	1811	125 (51.7)[d]	1823	159 (55.4)[d]	—
contralateral invasive breast cancer	1811	9 (4.1)[d]	1823	17 (5.9)[d]	—
secondary primary cancer (not breast cancer)	1811	33 (15.1)[d]	1823	35 (12.2)[d]	—
DCIS (ipsilateral or contralateral)	1811	8 (3.7)[d]	1823	13 (4.5)[d]	—
death from any cause	1811	21 (9.6)[d]	1823	17 (5.9)[d]	—
Disease-free survival	1811	219 (12.1) Median time to event: n. a. [n. c.; n. c.]	1823	287 (15.7) Median time to event: n. a. [n. c.; n. c.]	HR[a]: 0.75 [0.63; 0.90] 0.002
Symptomatology (EORTC QLQ-C30) - deterioration by ≥ 10 points (data cut-off: 19 December 2016)					
Fatigue					
End of anti-HER2 therapy	1538	703 (45.7)	1597	642 (40.2)	1.14 [1.05; 1.24] 0.001
36-month follow-up	1361	437 (32.1)	1327	474 (35.7)	0.90 [0.81; 1.00] 0.054
Nausea and vomiting					
End of anti-HER2 therapy	1542	184 (11.9)	1598	176 (11.0)	1.08 [0.89; 1.32] 0.411

36-month follow-up	1363	125 (9.2)	1328	132 (9.9)	0.92 [0.73; 1.15] 0.453
Pain					
End of anti-HER2 therapy	1541	420 (27.3)	1597	461 (28.9)	0.94 [0.84; 1.05] 0.297
36-month follow-up	1362	316 (23.2)	1328	318 (23.9)	0.97 [0.84; 1.11] 0.643
Dyspnoea					
End of anti-HER2 therapy	1539	392 (25.5)	1592	375 (23.6)	1.08 [0.96; 1.22] 0.214
36-month follow-up	1361	278 (20.4)	1321	303 (22.9)	0.90 [0.78; 1.03] 0.133
Insomnia					
End of anti-HER2 therapy	1538	430 (28.0)	1591	405 (25.5)	1.10 [0.98;1.24] 0.104
36-month follow-up	1362	318 (23.3)	1322	333 (25.2)	0.93 [0.81; 1.06] 0.279
loss of appetite					
End of anti-HER2 therapy	1538	235 (15.3)	1594	180 (11.3)	1.35 [1.13; 1.62] 0.001
36-month follow-up	1361	121 (8.9)	1326	125 (9.4)	0.95 [0.75; 1.20] 0.647
Constipation					
End of anti-HER2 therapy	1538	202 (13.1)	1593	248 (15.6)	0.84 [0.71; 1.00] 0.055
36-month follow-up	1363	219 (16.1)	1321	201 (15.2)	1.06 [0.89; 1.26] 0.537
Diarrhoea					
End of anti-HER2 therapy	1532	458 (29.9)	1590	213 (13.4)	2.23 [1.92; 2.58] < 0.001

36-month follow-up	1358	100 (7.4)	1322	128 (9.7)	0.76 [0.59; 0.97] 0.031
Symptomatology (EORTC QLQ-BR23) - deterioration by ≥ 10 points (data cut-off: 19 December 2016)					
Side effects of systemic therapy					
End of anti-HER2 therapy	1535	416 (27.1)	1591	426 (26.8)	1.02 [0.91; 1.14] 0.742
36-month follow-up	1358	313 (23.0)	1321	318 (24.1)	0.96 [0.83; 1.10] 0.522
Chest symptoms					
End of anti-HER2 therapy	1532	292 (19.1)	1580	246 (15.6)	1.23 [1.05; 1.43] 0.009
36-month follow-up	1355	154 (11.4)	1318	141 (10.7)	1.06 [0.85; 1.31] 0.610
Arm symptoms					
End of anti-HER2 therapy	1532	417 (27.2)	1581	454 (28.7)	0.94 [0.84; 1.05] 0.296
36-month follow-up	1355	320 (23.6)	1320	336 (25.5)	0.92 [0.81; 1.05] 0.227
Strain due to hair loss					
End of anti-HER2 therapy	57	10 (17.5)	54	16 (29.6)	0.59 [0.29; 1.19] 0.137[b]
36-month follow-up	73	18 (24.7)	77	20 (26.0)	0.89 [0.50; 1.58] 0.696

Health-related quality of life (data cut-off: 19 December 2016)

Endpoint	**Pertuzumab + trastuzumab + chemotherapy**		**Placebo + trastuzumab + chemotherapy**		Intervention vs Control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[c]
EORTC QLQ-C30 - deterioration by ≥ 10 points					

Global health status					
End of anti-HER2 therapy	1532	428 (27.9)	1589	421 (26.5)	1.05 [0.94; 1.18] 0.416
36-month follow-up	1357	295 (21.7)	1320	320 (24.2)	0.89 [0.78; 1.02] 0.106
Physical functioning					
End of anti-HER2 therapy	1543	358 (23.2)	1597	361 (22.6)	1.03 [0.90; 1.17] 0.664
36-month follow-up	1363	236 (17.3)	1329	234 (17.6)	0.98 [0.83; 1.15] 0.800
Role function					
End of anti-HER2 therapy	1540	383 (24.9)	1594	368 (23.1)	1.08 [0.95; 1.22] 0.221
36-month follow-up	1362	216 (15.9)	1327	243 (18.3)	0.87 [0.73; 1.03] 0.098
Emotional functioning					
End of anti-HER2 therapy	1535	388 (25.3)	1593	393 (24.7)	1.02 [0.91; 1.16] 0.715
36-month follow-up	1359	302 (22.2)	1324	337 (25.5)	0.87 [0.76; 1.00] 0.047
Cognitive functioning					
End of anti-HER2 therapy	1536	607 (39.5)	1592	632 (39.7)	1.00 [0.91; 1.09] 0.923
36-month follow-up	1360	490 (36.0)	1324	494 (37.3)	0.96 [0.87; 1.06] 0.436
Social functioning					
End of anti-HER2 therapy	1535	349 (22.7)	1590	376 (23.6)	0.96 [0.85; 1.09] 0.540
36-month follow-up	1360	209 (15.4)	1323	237 (17.9)	0.86 [0.73; 1.02] 0.085

EORTC QLQ-BR23 - deterioration by ≥ 10 points					
Body image					
End of anti-HER2 therapy	1521	407 (26.8)	1573	472 (30.0)	0.90 [0.80; 1.00] 0.056
36-month follow-up	1342	272 (20.3)	1304	300 (23.0)	0.88 [0.76; 1.02] 0.086
Sexual activity					
End of anti-HER2 therapy	1456	336 (23.1)	1509	358 (23.7)	0.97 [0.85; 1.11] 0.680
36-month follow-up	1279	258 (20.2)	1251	269 (21.5)	0.93 [0.80; 1.09] 0.377
Sex pleasure					
End of anti-HER2 therapy	437	147 (33.6)	481	159 (33.1)	1.02 [0.85; 1.23] 0.829
36-month follow-up	383	113 (29.5)	402	118 (29.4)	1.03 [0.83; 1.27] 0.822
Future prospects					
End of anti-HER2 therapy	1518	272 (17.9)	1576	292 (18.5)	0.97 [0.84; 1.13] 0.697
36-month follow-up	1340	191 (14.3)	1304	188 (14.4)	0.99 [0.82; 1.19] 0.918

Side effects (data cut-off: 19.06.2019)

Endpoint	**Pertuzumab + trastuzumab + chemotherapy**		**Placebo + trastuzumab + chemotherapy**		Intervention vs Control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Adverse events (presented additionally)					
	1783	1782 (> 99.9)	1822	1813 (99.5)	-
Serious adverse events (SAEs)					
	1783	509 (28.5)	1822	446 (24.5)	1.17 [1.05; 1.30] 0.006

Severe adverse events (CTCAE grade 3 or 4)					
	1783	1141 (64.0)	1822	1055 (57.9)	1.11 [1.05; 1.16] < 0.001
Therapy discontinuation due to adverse events					
	1783	219 (12.3)	1822	219 (12.0)	1.02 [0.86; 1.22] 0.809
Specific adverse events					
Diarrhoea (PT, AEs)	1783	1255 (70.4)	1822	824 (45.2)	1.56 [1.47; 1.65] < 0.001[b]
Pruritus (PT, AEs)	1783	258 (14.5)	1822	162 (8.9)	1.63 [1.35; 1.96] < 0.001[b]
Cardiac insufficiency (PT, SAEs)	1783	25 (1.4)	1822	13 (0.7)	1.97 [1.01; 3.83] 0.043[b]
Anaemia (PT, severe AEs)	1783	120 (6.7)	1822	86 (4.7)	1.43 [1.09; 1.87] 0.010[b]
Diarrhoea (PT, severe AEs)	1783	168 (9.4)	1822	71 (3.9)	2.42 [1.85; 3.17] < 0.001[b]
Stomatitis (PT, AEs)	1783	38 (2.1)	1822	18 (1.0)	2.16 [1.24; 3.77] 0.006[b]
Fatigue (PT, severe AEs)	1783	69 (3.9)	1822	49 (2.7)	1.44 [1.004; 2.06] 0.047[b]
Leukopenia (PT, severe AEs)	1783	91 (5.1)	1822	65 (3.6)	1.43 [1.05; 1.95] 0.024[b]
Metabolism and nutrition disorders (SOC, severe AEs)	1783	89 (5.0)	1822	47 (2.6)	1.94 [1.37; 2.74] < 0.001[b]
Musculoskeletal and connective tissue disorders (SOC, severe AEs)	1783	33 (1.9)	1822	55 (3.0)	0.61 [0.40; 0.94] 0.023[b]
Skin and subcutaneous tissue disorders (SOC, severe AEs)	1783	63 (3.5)	1822	36 (2.0)	1.79 [1.19; 2.68] 0.004[b]

[a] Cox model stratified by nodal status, type of adjuvant chemotherapy, hormone receptor status, and protocol version; p-value from stratified log-rank test
[b] 95 % CI asymptotic, unconditional exact test (CSZ method)
[c] RR and p-value from log-binomial regression adjusted for nodal status, type of adjuvant chemotherapy, hormone receptor status, and protocol version
[d] Data from additional analyses submitted by the pharmaceutical company in the context of the written statement
Abbreviations used: CTCAE: Common Terminology Criteria for Adverse Events; HR: Hazard ratio; CI Confidence interval; N: Number of patients evaluated; n: Number of patients with event; n.a.: not achieved; PT: Preferred Term; RR: relative risk; SOC: System Organ Class; SAE: serious adverse event; AE: adverse event; vs: versus

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

approx. 1,970 to 3,200 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 Phesgo (active ingredient: pertuzumab/trastuzumab) at the following publicly accessible link (last access: 7 April 2021):
https://www.ema.europa.eu/en/documents/product-information/phesgo-epar-product-information_de.pdf

Treatment with pertuzumab/trastuzumab 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.

Phesgo should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are immediately available.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pertuzumab/trastuzumab	€ 94,001.88
in combination with one of the following chemotherapy regimens:	
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC), docetaxel	
5-fluorouracil	€ 33.34 - € 66.68
Epirubicin	€ 1,403.25 - € 2,521.40
Cyclophosphamide	€ 47.75
Docetaxel	€ 3,270.36 - € 5,532.52

Designation of the therapy	Annual treatment costs/patient
Total	€ 98,756.58 - € 102,170.23
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC), paclitaxel (q1w)	
5-fluorouracil	€ 33.34 - € 66.68
Epirubicin	€ 1,403.25 - € 2,521.40
Cyclophosphamide	€ 47.75
Paclitaxel (q1w)	€ 5,135.52
Total	€ 100,621.74 €- 101,773.23 €
additionally required SHI services	*€ 216.40*
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), docetaxel	
5-fluorouracil	€ 33.34 - € 66.68
Doxorubicin	€ 851.25 - € 1,135.00
Cyclophosphamide	€ 47.75
Docetaxel	€ 3,270.36 - € 5,532.52
Total	€ 98,204.58- € 100,783.83
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), paclitaxel (q1w)	
5-fluorouracil	€ 33.34 - € 66.68
Doxorubicin	€ 851.25 - € 1,135.00
Cyclophosphamide	€ 47.75
Paclitaxel (q1w)	€ 5,135.52
Total	€ 100,069.74- € 100,386.83
additionally required SHI services	*€ 216.40*
+ doxorubicin + cyclophosphamide (AC), docetaxel	
Doxorubicin	€ 1,278.92
Cyclophosphamide	€ 47.75
Docetaxel	€ 3,270.36 - € 5,532.52
Total	€ 98,598.91- € 100,861.07
+ doxorubicin + cyclophosphamide (AC), paclitaxel (q1w)	
Doxorubicin	€ 1,278.92
Cyclophosphamide	€ 47.75
Paclitaxel (q1w)	€ 5,135.52
Total	€ 100,464.07
additionally required SHI services	*€ 216.40*
+ epirubicin + cyclophosphamide (EC), docetaxel	

Designation of the therapy	Annual treatment costs/patient
Epirubicin	€ 1,871.00 - € 2,521.40
Cyclophosphamide	€ 47.75
Docetaxel	€ 3,270.36 - € 5,532.52
Total	€ 99,190.99 - € 102,103.55
+ epirubicin + cyclophosphamide (EC), paclitaxel (q1w)	
Epirubicin	€ 1,871.00 - € 2,521.40
Cyclophosphamide	€ 47.75
Paclitaxel (q1w)	€ 5,135.52
Total	€ 101,056.15- € 101,706.55
additionally required SHI services	*€ 216.40*
+ docetaxel + carboplatin	
Docetaxel	€ 6,540.72
Carboplatin	€ 1,899.66
Total	€ 102,442.26
Appropriate comparator therapy:	
Trastuzumab	€ 37,481.87
in combination with one of the following chemotherapy regimens:	
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC), docetaxel	
5-fluorouracil	€ 33.34 - € 66.68
Epirubicin	€ 1,403.25 - € 2,521.40
Cyclophosphamide	€ 47.75
Docetaxel	€ 3,270.36 - € 5,532.52
Total	€ 42,236.57- € 45,650.22
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC), paclitaxel (q1w)	
5-fluorouracil	€ 33.34 - € 66.68
Epirubicin	€ 1,403.25 - € 2,521.40
Cyclophosphamide	€ 47.75
Paclitaxel (q1w)	€ 5,135.52
Total	€ 44,101.73- € 45,253.22
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), docetaxel	
5-fluorouracil	€ 33.34 - € 66.68
Doxorubicin	€ 851.25 - € 1,135.00
Cyclophosphamide	€ 47.75

Designation of the therapy	Annual treatment costs/patient
Docetaxel	€ 3,270.36 - € 5,532.52
Total	€ 41,684.57- € 44,263.82
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), paclitaxel (q1w)	
5-fluorouracil	€ 33.34 - € 66.68
Doxorubicin	€ 851.25 - € 1,135.00
Cyclophosphamide	€ 47.75
Paclitaxel (q1w)	€ 5,135.52
Total	€ 43,549.73- € 43,866.82
additionally required SHI services	*€ 216.40*
+ doxorubicin + cyclophosphamide (AC), docetaxel	
Doxorubicin	€ 1,278.92
Cyclophosphamide	€ 47.75
Docetaxel	€ 3,270.36 - € 5,532.52
Total	€ 42,078.90 - € 44,341.06
+ doxorubicin + cyclophosphamide (AC), paclitaxel (q1w)	
Doxorubicin	€ 1,278.92
Cyclophosphamide	€ 47.75
Paclitaxel (q1w)	€ 5,135.52
Total	€ 43,944.06
additionally required SHI services	*€ 216.40*
+ epirubicin + cyclophosphamide (EC), docetaxel	
Epirubicin	€ 1,871.00 - € 2,521.40
Cyclophosphamide	€ 47.75
Docetaxel	€ 3,270.36 - € 5,532.52
Total	€ 42,670.98- € 45,583.54
+ epirubicin + cyclophosphamide (EC), paclitaxel (q1w)	
Epirubicin	€ 1,871.00 - € 2,521.40
Cyclophosphamide	€ 47.75
Paclitaxel (q1w)	€ 5,135.52
Total	€ 44,536.14- € 45,186.54
additionally required SHI services	*€ 216.40*
+ docetaxel + carboplatin	
Docetaxel	€ 6,540.72

Designation of the therapy	Annual treatment costs/patient
Carboplatin	€ 2,088.36
Total	€ 46,110.95

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2021)

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Pertuzumab/ trastuzumab	not applicable				
in combination with one of the following chemotherapy regimens:					
5-fluorouracil + epirubicin + cyclophosphamide (FEC)	b	€ 81	2	6-8	€ 486 - € 648
+ docetaxel	b	€ 81	1	3 - 4	€ 243 - € 324
+ paclitaxel (q1w)	b	€ 81	3	12	€ 972
5-fluorouracil + doxorubicin + cyclophosphamide (FAC)	b	€ 81	2	6-8	€ 486 - € 648
+ docetaxel	b	€ 81	1	3 - 4	€ 243 - € 324
+ paclitaxel (q1w)	b	€ 81	1	12	€ 972
Doxorubicin + cyclophosphamide (AC)	b	€ 81	1	4	€ 324
+ docetaxel	b	€ 81	1	3 - 4	€ 243 - € 324
+ paclitaxel (q1w)	b	€ 81	1	12	€ 972
Epirubicin + cyclophosphamide (EC)	b	€ 81	1	4	€ 324
+ docetaxel	b	€ 81	1	3 - 4	€ 243 - € 324
+ paclitaxel (q1w)	b	€ 81	1	12	€ 972
Docetaxel + carboplatin	b	€ 81	2	12	€ 972
Appropriate comparator therapy:					
Trastuzumab	a	€ 71	1	18	€ 1,278
For the appropriate comparator therapy, the costs for the other SHI services of the chemotherapy regimens correspond to those of the medicinal product to be assessed.					
a: Surcharge for the preparation of a parenteral solution containing monoclonal antibodies b: Surcharge for the preparation of a parenteral preparation containing cytostatic agents					

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 15 July 2021.**

2. **The period of validity of the resolution is limited to 1 October 2022.**

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

Berlin, 15 July 2021

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

Prof. Hecken