Gemeinsamer Bundesausschuss

Justification

of the Resolution 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 Pertuzumab/trastuzumab (breast cancer, HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence, neoadjuvant)

of 15 July 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefits,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Costs of therapy for the statutory health insurance,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient pertuzumab/trastuzumab in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 February 2021. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 14 January 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de), on 3 May 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of pertuzumab/trastuzumab compared with the appropriate comparator therapy could be determined on the basis of the

dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of pertuzumab/trastuzumab.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of pertuzumab/trastuzumab (Phesgo) according to product information

Phesgo is indicated for use in combination with chemotherapy in:

- the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence

Therapeutic indication of the resolution (resolution of 15.07.2021):

see approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence

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

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.

[1] AGeneral Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. With regard to the authorisation status, the following active ingredients are available for the neoadjuvant treatment of HER2-positive, early breast cancer with a high risk of recurrence: docetaxel, doxorubicin, epirubicin, 5-fluorouracil, paclitaxel, vincristine, trastuzumab and pertuzumab (in combination with trastuzumab).

Medicinal products with explicit marketing authorisation for the treatment of hormone-receptor positive breast cancer or in the context of endocrine therapy were not included.

on 2. A non-medicinal treatment cannot be considered as a comparator therapy in this therapeutic indication.

on 3. The following resolutions or guidelines of the G-BA for medical products and non-medicinal treatments are available:

Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V:
- Pertuzumab – Resolution of 18 February 2016

Methods Hospital Treatment Policy - Section 4 Excluded Methods, effective 19 December 2019:
- Proton therapy for breast cancer

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

Current national and international guidelines for the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory or early stage breast cancer unanimously recommend therapy with trastuzumab directed against HER2. Trastuzumab is to be integrated into a chemotherapy regimen that includes a taxane (paclitaxel or docetaxel) and, if appropriate, an anthracycline (doxorubicin or epirubicin).

The underlying guidelines list various anthracycline-free and anthracycline-containing treatment protocols that are generally considered appropriate treatment options. However, the implementation of an anthracycline-containing treatment protocol must be weighed against the cardiovascular risks. Trastuzumab should not be used in combination with an anthracycline but sequentially in combination with a taxane. Cardiac functions should be monitored closely.

The active ingredient pertuzumab was evaluated within the framework of the benefit assessment according to Section 35a SGB V. Pertuzumab is indicated for use in

combination with trastuzumab and chemotherapy for neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence. By resolution of the G-BA of 18 February 2016, it was determined for pertuzumab in the neoadjuvant therapy situation that the additional benefit compared to the appropriate comparator therapy is not proven, as no robust, statistically significant differences between the treatment arms were shown with regard to the patient-relevant endpoints used within the NeoSphere study. In the overall consideration of the available evidence, the active ingredient pertuzumab is not determined to be an appropriate comparator therapy.

In determining the appropriate comparator therapy, medicinal products with explicit marketing authorisation for the treatment of hormone-receptor positive breast cancer were not considered. However, patients with positive hormone receptor status are expected to receive endocrine therapy in addition to standard neoadjuvant chemotherapy with trastuzumab.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of pertuzumab/trastuzumab in combination with chemotherapy is assessed as follows:

An additional benefit is not proven for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

Justification:

In the context of the marketing authorisation of the subcutaneous (s.c.) fixed combination of pertuzumab/trastuzumab, the pharmaceutical company proved the bioequivalence and active equivalence of the s.c. fixed combination and the free intravenous combination of pertuzumab + trastuzumab with the FeDeriCa study. The pharmaceutical company therefore derives the additional benefit independently of the dosage form. To prove the additional benefit of the s.c. fixed combination pertuzumab/trastuzumab for the neoadjuvant treatment of adults with HER2-positive locally advanced, inflammatory or early stage breast cancer at high risk of recurrence, the pharmaceutical company, therefore, presents the results of the NeoSphere study, which also formed the basis of the benefit assessment already carried out on pertuzumab in free combination with trastuzumab[2]. The G-BA considers these data to be suitable and bases the present benefit assessment on them. Furthermore, the pharmaceutical company submitted data from the PEONY study.

The PEONY study is not used for the present benefit assessment. The adjuvant treatment phase of the study investigated different treatment regimens, and consequently, the study results cannot be attributed to the neoadjuvant treatment phase. Furthermore, the available data cut-off does not contain relevant data for the benefit assessment.

The NeoSphere study is a multicenter, open-label, randomised controlled phase II trial that enrolled adults (N=417) with HER2-positive locally advanced, inflammatory, or early stage

[2] https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/188/

invasive breast cancer with a primary tumour diameter > 2 cm and an Eastern Cooperative Oncology Group Performance Status≤ 1.

The study was conducted in 59 study sites in 16 countries in Europe, North and South America, and Asia-Pacific.

The study compared pertuzumab in combination with trastuzumab and docetaxel (arm A, N = 107) or trastuzumab in combination with docetaxel (arm B, N = 107) or pertuzumab in combination with trastuzumab (arm C, N = 107) or pertuzumab in combination with docetaxel (arm D, N = 96) as part of neoadjuvant treatment. Relevant for the benefit assessment are study arms A and B, in which pertuzumab was used in the approved combination therapy, or the appropriate comparator therapy for the neoadjuvant treatment phase was adequately implemented with regard to the active ingredients used. Study participants each received 4 cycles of neoadjuvant therapy at 3-week intervals, followed by breast surgery and adjuvant drug therapy (trastuzumab in combination with 3 cycles of 5-fluorouracil, epirubicin, and cyclophosphamide).

The primary endpoint of the study was pathological complete remission (pCR). Furthermore, the endpoints recurrence, breast-conserving surgery, and adverse events, including deaths, were collected.

The transferability of the study results to the German health care context is limited by the fact that trastuzumab was used in adjuvant therapy at the same time as anthracycline-containing chemotherapy, contrary to the recommendations of the product information, and not sequentially due to the increased cardiotoxic risk. In addition, chemotherapy was divided into a neoadjuvant and adjuvant part, which is discouraged in guidelines with few exceptions.

Arms A and B of the NeoSphere study could nevertheless be used for the assessment of the additional benefit, as all components of the combination therapy recommended in the guidelines were used in adequate doses. In summary, the study results with regard to the dosage regimen and treatment intervals are considered to be sufficiently transferable to the German health care context.

Extent and probability of the additional benefit

Mortality

For the endpoint overall survival no statistically significant difference was detected between the study arms relevant to the assessment (arm A: pertuzumab + trastuzumab + docetaxel, arm B: trastuzumab + docetaxel)

Mortality results are based on the number of deaths recorded in the adverse event assessment. It is not comprehensible why the overall mortality in an oncological indication was only assessed in the context of side effects and not systematically as an independent endpoint of efficacy.

No additional benefit is determined for the endpoint overall survival.

Morbidity

Recurrences (recurrence rate and disease-free survival)

Patients in the therapeutic indication are treated with a curative therapy approach: adjuvant therapy after complete resection of the primary tumours and possibly affected lymph nodes. Nevertheless, remaining tumour cells can cause a recurrence in the further course. Recurrence

means that the attempt at a cure by the curative therapeutic approach was unsuccessful. The occurrence of a recurrence is patient-relevant.

In the present benefit assessment, recurrences were taken into account in the endpoint recurrence rates as well as in the endpoint disease-free survival. In both analyses, there was no statistically significant difference between the two study arms used.

With regard to the recurrent rate and disease-free survival, an additional benefit of pertuzumab + trastuzumab compared with the appropriate comparator therapy is not proven.

Breast-conserving surgeries

Statistically, the proportion of patients who, in the opinion of the study physician, could undergo breast-conserving surgery after neoadjuvant therapy was not significantly different between treatment arms.

For the endpoint breast-conserving surgeries, an additional benefit is not proven.

Pathological complete remission

The primary endpoint of the NeoSphere study was pathological complete remission, for which there was a statistically significant difference between the two arms relevant to the evaluation.

Pathological complete remission (pCR) is considered a surrogate endpoint of unclear validity. The results of the validation studies submitted by the pharmaceutical company by Cortazar et al.[3] and von Minckwitz et al.[4] show that although there is an overall association between pCR and overall mortality at the patient-individual level, evidence of a correlation of the results was not provided at the study level. The analyses also show that different patient populations with different molecular subtypes (e.g. luminal B-like vs HER2-positive-like), also benefit differently from pCR on a patient-individual level. Themeta-analysis presented by Spring et al.[5] is also not suitable to prove the surrogate validity of pCR for the endpoints overall survival and event-free survival. The meta-analysis describes only an association of pCR and patient-relevant endpoints at the individual level and no correlation of effects.

In the NeoSphere study, several molecular subtypes were investigated so that the transferability of the results of the validation studies to the study population and consequently to the target population in the therapeutic indication is limited.

Overall, sufficient validation of a surrogate endpoint usually requires evidence of both patient-level and study-level correlation. As this is not the case for the present endpoint, the pCR cannot be used to assess the additional benefit.

In addition, beyond the insufficient surrogate validation, it is unclear at this stage how a difference of 17.8% in the proportion of patients with pathological complete remission between the study arms is relevant. The NeoSphere study did not show that the different proportion of patients with pCR translated statistically into a significantly different proportion of patients with recurrence. Similarly, there is little difference in terms of overall survival in either patient group.

[3] Cortazar, Patricia, et al. "Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis." The Lancet 384.9938 (2014): 164172

[4] Von Minckwitz, Gunter, et al. "Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes." Journal of Clinical Oncology (2012): JCO-2011.

[5] Spring LM et al. Pathologic Complete Response after Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Survival: A Comprehensive Meta-analysis. Clin Cancer Res 2020; 26(12): 28382848

Quality of life

Data on health-related quality of life were not collected in the NeoSphere study.

Side effects

The data of the NeoSphere study exclusively depict the side effects of the free intravenous combination of pertuzumab + trastuzumab. Adverse events directly attributable to the subcutaneous application of the fixed combination could not be recorded in this study.

Adverse events

Except for two patients in the pertuzumab arm, an adverse event was documented in all patients in the study arms considered. The presentation of the overall rate of adverse events is only supplementary.

Severe adverse events (CTCAE ≥ grade 3)

There is no statistically significant difference between the treatment arms.

Serious adverse events

There is no statistically significant difference between the treatment arms.

Discontinuation because of adverse events

Therapy discontinuation due to adverse events occurred in six patients in the intervention arm. No therapy discontinuations were recorded in the comparator arm. The difference between the treatment arms is statistically significant to the disadvantage of pertuzumab + trastuzumab.

Consideration of the six therapy discontinuations in the intervention arm showed that four patients had an adverse event in the form of left ventricular dysfunction with a reduction in ejection fraction to below 50%. The event occurred in three patients after completion of pertuzumab treatment in the subsequent adjuvant treatment phase and only one patient during neoadjuvant therapy. According to previous findings, also from the studies with pertuzumab in metastatic breast cancer (CLEOPATRA study) and the longer treatment duration, there is no evidence of delayed cardiotoxicity of pertuzumab. Furthermore, an increased risk of cardiovascular side effects was also reported for treatment with trastuzumab and anthracyclines administered in adjuvant therapy, further complicating the interpretability of the results.

One therapy discontinuation due to an adverse event occurred in the neoadjuvant treatment phase as a result of intolerance to docetaxel, although treatment with pertuzumab could be continued. The therapy of another patient was discontinued due to a strangulated abdominal hernia. It is unclear to what extent these events are attributable to pertuzumab treatment.

In the overall analysis, the increased number of treatment discontinuations is not reflected in the overall rates of SAEs and severe AEs CTCAE ≥ grade 3. Furthermore, there are low case numbers in the NeoSphere study and unclear causality. Overall, the statistically significant difference between the treatment arms can therefore not be attributed to pertuzumab with sufficient certainty, so that for the endpoint side effects, an additional benefit or a lesser benefit is not proven.

Overall assessment/conclusion

In the present benefit assessment, the s.c. fixed combination pertuzumab/trastuzumab is evaluated. In the context of the marketing authorisation of the s.c fixed combination, bioequivalence and efficacy were demonstrated in comparison to the free intravenous

combination of pertuzumab + trastuzumab. This evaluation is therefore based on the free combination data from the NeoSphere study.

For the assessment of the additional benefit of pertuzumab/trastuzumab in combination with chemotherapy, results on mortality (overall survival), morbidity, and side effects are available from the NeoSphere study.

The relevant sub-population of the study was considered those treatment arms of the NeoSphere study in which pertuzumab + trastuzumab was used in the approved combination therapy or in which the appropriate comparator therapy for the neoadjuvant treatment phase was adequately implemented concerning the active ingredients used.

For the endpoints overall survival, recurrences, breast-conserving surgery and side effects, the results of the NeoSphere study showed no robust, statistically significant differences between the treatment arms. Data on health-related quality of life were not collected in the NeoSphere study.

In the overall analysis of the results on mortality, morbidity and side effects, there is no additional benefit and no reduced benefit of pertuzumab in the neoadjuvant therapy of HER2-positive locally advanced, inflammatory or early stage breast cancer with a high risk of recurrence compared with the appropriate comparator therapy. Thus, the G-BA states that for the s.c. fixed combination pertuzumab/trastuzumab in combination with chemotherapy compared with trastuzumab in combination with a taxane and an anthracycline, if appropriate, an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Phesgo with the s.c. fixed combination pertuzumab/trastuzumab in combination with chemotherapy.

The combination of active ingredients pertuzumab/trastuzumab is approved for the neoadjuvant treatment of adult patients with HER2-positive locally advanced, inflammatory or early stage breast cancer at high risk of recurrence.

A therapy regimen containing trastuzumab, a taxane (paclitaxel or docetaxel), and, if applicable, an anthracycline (doxorubicin or epirubicin) was determined by the G-BA as an appropriate comparator therapy.

For the assessment of the additional benefit of pertuzumab/trastuzumab in combination with chemotherapy, results are available from the NeoSphere study in comparison with trastuzumab + chemotherapy.

For the endpoints overall survival, recurrences, breast-conserving surgery and side effects, the results of the NeoSphere study showed no robust, statistically significant differences between the treatment arms. Data on health-related quality of life were not collected in the NeoSphere study.

In the overall analysis of the results on mortality, morbidity and side effects, there is no additional benefit and no reduced benefit of pertuzumab in the neoadjuvant therapy of HER2-positive locally advanced, inflammatory or early stage breast cancer with a high risk of recurrence compared with the appropriate comparator therapy. Thus, the G-BA states that for the s.c. fixed combination pertuzumab/trastuzumab in combination with chemotherapy compared with trastuzumab in combination with a taxane and an anthracycline, if appropriate, an additional benefit is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier. The range of 2690 to 3450 persons given here considers uncertainties in the data and reflects the minimum and maximum values obtained when deriving the patient numbers. Due to the existing uncertainty of the data basis, a more precise indication is not possible.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 June 2021).

For the presentation of the treatment costs and the consumption of the chemotherapy component of the combination treatment with pertuzumab, only the active ingredients listed in the context of the appropriate comparator therapy are considered for better comparability.

Pertuzumab/trastuzumab

For the isolated consideration of the neoadjuvant therapy with pertuzumab/trastuzumab relevant for the evaluation, a treatment over 3 to 6 cycles, each at intervals of 3 weeks (21 days), is assumed for the presentation of consumption and treatment costs. The adjuvant therapy that may follow is not considered.

Trastuzumab

The data on trastuzumab are based on the intravenous (i.v.) application.

The information on dosages refers to applications in women, as breast cancer is relatively rare in men. Body surface area is calculated using the Du Bois formula using average body weight

for women of 68.7 kg and an average height of 1.66 m according to the 2017 microcensus = 1.76 m².[6]

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Pertuzumab/ trastuzumab	Once every 21 days	3 - 6	1	3 - 6
Docetaxel	Once every 21 days	3 - 6	1	3 - 6
Paclitaxel	Once every 21 days	3 - 6	1	3 - 6
Doxorubicin	Once every 21 days	3 - 6	1	3 - 6
Epirubicin	Once every 21 days	3 - 6	1	3 - 6
Appropriate comparator therapy				
Trastuzumab	3-weekly application			
	Once every 21 days	3 - 6	1	3 - 6
	weekly application[7]			
	Once every 7 days	9 - 18	1	9 - 18
Docetaxel	Once every 21 days	3 - 6	1	3 - 6
Paclitaxel	Once every 21 days	3 - 6	1	3 - 6
Doxorubicin	Once every 21 days	3 - 6	1	3 - 6
Epirubicin	Once every 21 days	3 - 6	1	3 - 6

Consumption:

[6] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

[7] Weekly application and dosage of trastuzumab in combinations with docetaxel according to trastuzumab's product information (last revised: March 2021).

Designation of the therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Pertuzumab/ trastuzumab	Cycle 1: 1,200 mg/600 mg From cycle 2 onwards: 600 mg/600 mg	1,200 mg/600 mg 600 mg/600 mg	1 x 1,200 mg/600 mg 1 x 600 mg/600 mg	3 – 6	1 x 1,200 mg/600 mg + 2 x 600 mg/600 mg - 1 x 1,200 mg/600 mg + 5 x 600 mg/600 mg
Docetaxel	Cycle 1: 75 mg/m^2 From cycle 2 onwards: 75 mg/m^2 - 100 mg/m^2	132 mg - 132 mg - 176 mg	1 x 140 mg - 1 x 140 mg - 1 x 160 mg + 1 x 20 mg	3 – 6	3 x 140 mg - 1 x 140 mg + 5 x 160 mg + 5 x 20 mg
Paclitaxel	175 mg/m² 175 mg/m²	308 mg 308 mg	1 x 300 mg + 1 x 30 mg - 1 x 300 mg + 1 x 30 mg	3 – 6	3 x 300 mg + 3 x 30 mg - 6 x 300 mg + 6 x 30 mg
Doxorubicin	30 mg/m^2 60 mg/m^2	52.8 mg - 105.6 mg	1 x 50 mg + 1 x 10 mg - 1 x 100 mg + 1 x 10 mg	3 – 6	3 x 50 mg + 3 x 10 mg - 6 x 100 mg + 6 x 10 mg
Epirubicin	60 mg/m^2 90 mg/m^2	105.6 mg - 158.4 mg	1 x 100 mg + 1 x 10 mg - 1 x 100 mg + 1 x 50 mg + 1 x 10 mg	3 – 6	3 x 100 mg + 3 x 10 mg - 6 x 100 mg + 6 x 50 mg + 6 x 10 mg
Appropriate comparator therapy					
Trastuzumab	3-weekly application				
	Cycle 1: 8mg/kg From cycle 2 onwards: 6mg/kg	549.6 mg 412.2 mg	1 x 420 mg + 1 x 150 mg – 1 x 420 mg + 1 x 150 mg	3 – 6	3 x 420 mg + 1 x 150 mg - 6 x 420 mg + 1 x 150 mg
	weekly application[7]				
	Cycle 1: 4mg/kg From cycle 2 onwards: 2mg/kg	274.8 mg 137.4 mg	2 x 150 mg - 1 x 150 mg	9 - 18	10 x 150 mg - 19 x 150 mg

Designation of the therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Docetaxel	Cycle 1: 75 mg/m² From cycle 2 onwards: 75 mg/m² - 100 mg/m²	132 mg - 132 mg - 176 mg	1 x 140 mg - 1 x 140 mg - 1 x 160 mg + 1 x 20 mg	3 – 6	3 x 140 mg - 1 x 140 mg + 5 x 160 mg + 5 x 20 mg
Paclitaxel	175 mg/m² 175 mg/m²	308 mg 308 mg	1 x 300 mg + 1 x 30 mg - 1 x 300 mg + 1 x 30 mg	3 – 6	3 x 300 mg + 3 x 30 mg - 6 x 300 mg + 6 x 30 mg
Doxorubicin	30 mg/m² 60 mg/m²	52.8 mg - 105.6 mg	1 x 50 mg + 1 x 10 mg - 1 x 100 mg + 1 x 10 mg	3 – 6	3 x 50 mg + 3 x 10 mg - 6 x 100 mg + 6 x 10 mg
Epirubicin	60 mg/m² 90 mg/m²	105.6 mg - 158.4 mg	1 x 100 mg + 1 x 10 mg - 1 x 100 mg + 1 x 50 mg + 1 x 10 mg	3 – 6	3 x 100 mg + 3 x 10 mg - 6 x 100 mg + 6 x 50 mg + 6 x 10 mg

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pertuzumab/ trastuzumab 1,200 mg/600 mg	1 SFI	€ 8,107.65	€ 1.77	€ 459.75	€ 7,646.13
Pertuzumab/ trastuzumab 600 mg/600 mg	1 SFI	€ 5,385.83	€ 1.77	€ 304.31	€ 5,079.75
Docetaxel 140 mg	1 CIS	€ 1,145.74	€ 1.77	€ 53.85	€ 1,090.12
Docetaxel 160 mg	1 CIS	€ 1,397.36	€ 1.77	€ 175.44	€ 1,220.15
Docetaxel 20 mg	1 CIS	€ 172.41	€ 1.77	€ 7.66	€ 162.98
Paclitaxel 300 mg	1 CIS	€ 891.00	€ 1.77	€ 41.76	€ 847.47
Paclitaxel 30 mg	1 CIS	€ 101.89	€ 1.77	€ 4.31	€ 95.81

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Doxorubicin 10 mg[8]	1 CIS	€ 40.04	€ 1.77	€ 2.29	€ 35.98
Doxorubicin 50 mg[8]	1 CIS	€ 150.99	€ 1.77	€ 11.07	€ 138.15
Doxorubicin 100 mg[8]	1 CIS	€ 285.52	€ 1.77	€ 0.00	€ 283.75
Epirubicin 10 mg	1 CIS	€ 39.23	€ 1.77	€ 1.34	€ 36.12
Epirubicin 50 mg	1 CIS	€ 155.18	€ 1.77	€ 6.84	€ 146.57
Epirubicin 100 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Appropriate comparator therapy					
Trastuzumab 420 mg	1 PIC	€ 2,163.13	€ 1.77	€ 120.26	€ 2,041.10
Trastuzumab 150 mg	1 PIC	€ 786.79	€ 1.77	€ 42.95	€ 742.07
Docetaxel 140 mg	1 CIS	€ 1,145.74	€ 1.77	€ 53.85	€ 1,090.12
Docetaxel 160 mg	1 CIS	€ 1,397.36	€ 1.77	€ 175.44	€ 1,220.15
Docetaxel 20 mg	1 CIS	€ 172.41	€ 1.77	€ 7.66	€ 162.98
Paclitaxel 300 mg	1 CIS	€ 891.00	€ 1.77	€ 41.76	€ 847.47
Paclitaxel 30 mg	1 CIS	€ 101.89	€ 1.77	€ 4.31	€ 95.81
Doxorubicin 10 mg[8]	1 CIS	€ 40.04	€ 1.77	€ 2.29	€ 35.98
Doxorubicin 50 mg[8]	1 CIS	€ 150.99	€ 1.77	€ 11.07	€ 138.15
Doxorubicin 100 mg[8]	1 CIS	€ 285.52	€ 1.77	€ 0.00	€ 283.75
Epirubicin 10 mg	1 CIS	€ 39.23	€ 1.77	€ 1.34	€ 36.12
Epirubicin 50 mg	1 CIS	€ 155.18	€ 1.77	€ 6.84	€ 146.57
Epirubicin 100 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIC = powder for the preparation of an infusion solution concentrate					

LAUER-TAXE® last revised: 15 June 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

[8]Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Days of treatment / year	Costs/ patient/ year
Paclitaxel							
Dexamethasone 2 x 20 mg[8]	10 TAB à 20 mg	€ 32.14	€ 1.77	€ 0.00	€ 30.37	3 –	€ 30.37 -
	20 TAB à 20 mg	€ 53.81	€ 1.77	€ 0.00	€ 52.04	6	€ 52.04
Dimetindene i.v. 1 mg/10 kg	5 SFI 4 mg each	€ 18.62	€ 1.77	€ 1.92	€ 14.93	3 – 6	€ 29.86 - € 44.79
Cimetidine i.v. 300 mg[8]	10 AMP 200 mg each	€ 21.55	€ 1.77	€ 0.00	€ 19.78	3 – 6	€ 19.78 - € 39.56
Abbreviations: AMP = ampoules; SFI = solution for injection; TAB = tablets							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (contract on price formation for substances and preparation of substances) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy retail price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 21 April 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 January 2021, the pharmaceutical company submitted a dossier for the benefit assessment of pertuzumab/trastuzumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 18 January 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pertuzumab/trastuzumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 April 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 3 May 2021. The deadline for submitting written statements was 25 May 2021.

The oral hearing was held on 7 June 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 July 2021, and the proposed resolution was approved.

At its session on 15 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	21 April 2020	Determination of the appropriate comparator therapy
Working group Section 35a	1 June 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	7 June 2021	Conduct of the oral hearing
Working group Section 35a	15 June 2021 29 June 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	6 July 2021	Concluding discussion of the draft resolution
Plenum	15 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 July 2021

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

Prof. Hecken