Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Pertuzumab/ Trastuzumab (reassessment after the deadline: breast cancer, HER2+, early at high risk of recurrence, adjuvant treatment, combination with chemotherapy)

of 16 March 2023

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 benefit,
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. treatment costs for the statutory health insurance funds,
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 online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the combination of active ingredients pertuzumab/ trastuzumab (Phesgo) to be assessed for the first time on 14 January 2021. For the resolution of 15 July 2021 made by the G-BA in this procedure, a limitation up to 1 October 2022 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Phesgo recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 27 September 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 January 2023 on the G-BA website (www.g-ba.de), 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 the product information

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

Therapeutic indication of the resolution (resolution of 16 March 2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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)

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.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA 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. In relation to the authorisation status, in addition to pertuzumab/ trastuzumab, the active ingredients cyclophosphamide, docetaxel, doxorubicin, epirubicin, 5-fluorouracil, methotrexate, paclitaxel, pertuzumab, vincristine, trastuzumab, trastuzumab emtansine are available for the adjuvant treatment of HER2 positive, early stage breast cancer at high risk of recurrence.

The marketing authorisation of trastuzumab includes its use in combination with docetaxel and carboplatin for adjuvant chemotherapy. In other constellations, carboplatin is not prescribable.

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 radiotherapy is generally considered as a non-medicinal treatment in the present 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 20 December 2018

Methods Hospital Treatment Policy - Section 4 Excluded Methods, effective 19 December 2019:

- Proton therapy for breast cancer

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the “Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V”.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

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 care.

Current national and international guidelines for the adjunctive therapy of HER2-positive 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). Trastuzumab should be administered over a period of one year.

The underlying guidelines list various anthracycline-free and anthracycline-containing treatment protocols that are generally eligible as appropriate comparator therapy. 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.

By G-BA's resolution of 20 December 2018, a hint of a minor additional benefit was identified for pertuzumab in combination with trastuzumab and chemotherapy compared with the appropriate comparator therapy – a therapy regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if appropriate, an anthracycline (doxorubicin or epirubicin). The period of validity of the resolution was limited to 1. October 2022. A new benefit assessment is currently being carried out after the deadline. For the present resolution, pertuzumab in combination with trastuzumab and chemotherapy 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, it is assumed that patients with positive hormone receptor status receive endocrine therapy in addition to standard adjuvant chemotherapy with trastuzumab.

A therapy regimen containing trastuzumab, a taxane (paclitaxel or docetaxel), and, if applicable, an anthracycline (doxorubicin or epirubicin) is determined to be an appropriate comparator therapy for the present benefit assessment.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of pertuzumab/ trastuzumab is assessed as follows:

For pertuzumab/ trastuzumab in combination with chemotherapy for the adjuvant treatment of adults with HER2-positive early stage breast cancer at high risk of recurrence, there is an indication of a minor additional benefit.

Justification:

Within the scope of the marketing authorisation of the subcutaneous (SC) fixed combination of pertuzumab/ trastuzumab, the pharmaceutical company proved the bio-equivalence and efficacy equivalence of the SC fixed combination pertuzumab/ trastuzumab and the free

intravenous (IV) combination pertuzumab + trastuzumab with the FeDeriCa study. It therefore derives the additional benefit independently of the form of administration and therefore presents the results of the APHINITY study for the proof of the additional benefit of pertuzumab/ trastuzumab, which was also the basis of the already carried out benefit assessment of pertuzumab in free combination with trastuzumab[2]. The G-BA considers these data to be suitable and bases the present benefit assessment on them.

The APHINITY study is a multicentre, double-blind, randomised study comparing pertuzumab + trastuzumab + chemotherapy with placebo + trastuzumab + chemotherapy regimen. Adults with HER2-positive early breast cancer were enrolled in the ongoing global study. Primary tumours and any affected lymph nodes were completely resected surgically prior to the start of the study.

4805 patients enrolled were randomised 1:1 to the pertuzumab + trastuzumab + chemotherapy arm and to the placebo + trastuzumab + chemotherapy arm. Prior to randomisation, the principal investigator selected a chemotherapy regimen from those available (both with or without anthracyclines). The 52-week anti-HER2 therapy started at the same time as the taxane-containing chemotherapy. The comparator therapy used in the control arm of the study corresponds to the appropriate comparator therapy: a therapy regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if necessary, an anthracycline (doxorubicin or epirubicin).

For the benefit assessment, the relevant sub-population of adults at high risk of recurrence (node-positive and hormone receptor-negative) is considered in accordance with the approved therapeutic indication of pertuzumab, with n = 1811 adults in the intervention arm and n = 1823 adults. The pharmaceutical company shall present the study results for this sub-population in their dossier.

The APHINITY study is being conducted from September 2011 in 548 study sites in 42 countries in North and South America, Europe, South Africa and Asia.

The primary study endpoint is invasive disease-free survival. In addition, data on mortality, morbidity (symptomatology (EORTC QLQ-C30 and QLQ-BR23), quality of life (EORTC QLQ-C30 and QLQ-BR23) and side effects are collected.

The pharmaceutical company presents the results with the data cut-offs of 19.12.2016, 19.06.2019 and 10.01.2022 in the dossier. For the present benefit assessment, the endpoint categories of mortality, morbidity (recurrences) and side effects of the 3rd data cut-off (10.01.2021) are used. The assessment of morbidity (symptomatology) and health-related quality of life is based on the primary data cut-off (19.12.2016), as all patients had already completed the treatment phase and the last planned collection of questionnaires at this data cut-off.

Extent and probability of the additional benefit

Mortality

Overall survival

Overall survival is defined in the APHINITY study as the time between randomisation and death, regardless of the underlying cause of death.

For this endpoint, there is a statistically significant difference between the treatment arms in favour of pertuzumab + trastuzumab + chemotherapy. The median survival time has not yet

[2] https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/376/

been reached in either treatment group. During interpretation, it should be taken into account that a relevant percentage of patients with relapse in the comparator arm of the APHINITY study is to be assumed to have received inadequate subsequent therapy with respect to the current therapy standard. According to the information on subsequent therapies submitted by the pharmaceutical company in the written statement procedure, only about 45% of patients with relapse received subsequent therapy with a therapy directed against HER2. Evidence and guideline recommendations for initial systemic therapy after recurrence indicate a recommendation for therapy directed against HER2.

Due to the small extent and the questionable validity of the observed effect in the mortality endpoint category, neither an advantage nor a disadvantage of pertuzumab in the mortality endpoint category is determined in the overall assessment against the background of the uncertainties of the study with regard to the subsequent therapies and thus, the transferability to the German healthcare context.

Morbidity

Recurrences (recurrence rate and disease-free survival)

Patients in the present therapeutic indication are treated with a curative therapeutic approach. The failure of a curative therapeutic approach is fundamentally patient-relevant. The significance of the endpoints on recurrences depends on the extent to which the selected individual components are suitable for adequately reflecting the failure of potential cure by the present curative therapeutic approach.

In the present benefit assessment, recurrences are taken into account in the endpoint of recurrence rate as well as in the endpoint of disease-free survival. Both evaluations include the following events:

- Ipsilateral invasive local breast cancer recurrence
- Ipsilateral invasive regional breast cancer recurrence
- Distant recurrence
- Contralateral invasive breast cancer
- Secondary primary cancer (not breast cancer)
- Ductal cancer in situ (ipsilateral or contralateral)
- Ipsilateral or contralateral DCIS
- Death from any cause

In the present therapeutic indication, this operationalisation is suitable to depict a failure of the potential cure by the curative therapeutic approach.

At the present data cut-off, the median time to recurrence event has not been reached in either treatment group. The absolute difference in terms of recurrence rate is 4.9% (140 events out of 1,811 (7.7%) vs 175 events out of 1,823 (9.6%) patients). In the consideration of both endpoints, an overall relevant advantage of pertuzumab + trastuzumab + chemotherapy over trastuzumab + chemotherapy is found with regard to the avoidance of recurrences.

Symptomatology

Symptomatology was assessed in the APHINITY study using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module QLQ-BR23.

For the assessment, the proportion of patients with a deterioration of ≥ 10 points is used. Two different points in time are considered: End of anti-HER2 therapy and 36-month follow-up.

For the endpoints of fatigue and chest symptoms, statistically significant disadvantages are only present at the end of anti-HER2 therapy.

For the endpoint of diarrhoea at the end of anti-HER2 therapy, there is initially a statistically significant disadvantage. At 36-month follow-up, however, there is a statistically significant advantage.

For the other presented endpoints, no statistically significant differences are detected between the study arms.

In summary, with regard to the endpoints on symptomatology, there are only statistically significant disadvantages in individual endpoints right at the end of anti-HER2 therapy. These disadvantages are no longer evident at the 36-month follow-up; there is even a statistically significant advantage for the endpoint of diarrhoea. Overall, neither an advantage nor a disadvantage of pertuzumab + trastuzumab + chemotherapy with regard to symptomatology can be determined.

Quality of life

Health-related quality of life was assessed in the APHINITY study using the functional scales of the EORTC QLQ-C30 and EORTC-QLQ-BR23 questionnaires.

For the assessment, the proportion of patients with a deterioration of ≥ 10 points is used. Two different points in time are considered: End of anti-HER2 therapy and 36-month follow-up.

For the endpoint emotional functioning, there was a statistically significant difference in benefit of pertuzumab + trastuzumab + chemotherapy at 36-month follow-up.

There were no statistically significant differences in the other endpoints.

In summary, in the quality of life category, there are no advantages or disadvantages of pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy.

Side effects

Adverse events (AEs)

In the APHINITY study, AEs occurred in both study arms in almost all patients enrolled. The results were only presented additionally.

Serious adverse events (SAEs)

There is a statistically significant disadvantage of pertuzumab + trastuzumab + chemotherapy for serious adverse events.

Severe AEs (CTCAE grade 3 or 4)

There is a statistically significant disadvantage of pertuzumab + trastuzumab + chemotherapy over trastuzumab + chemotherapy with regard to severe adverse events with CTCAE grade ≥ 3.

In the subgroup analysis by region (subgroups USA / Canada, Asia / Pacific, Western Europe, Latin America, others), statistically significant differences are only found for the regions USA / Canada and Asia / Pacific, but not for the region Western Europe. Although the region of Western Europe is the relevant region for the coverage area of the present benefit assessment, it does not seem appropriate in the present case to focus solely on this subgroup for the assessment of the results on severe AEs, especially since this subgroup effect is not supported by the available study results overall.

Discontinuation due to AEs

For the endpoint therapy discontinuation due to AE, no statistically significant difference was detected between the treatment arms.

Specific AEs

There is a statistically significant advantage of pertuzumab + trastuzumab + chemotherapy over trastuzumab + chemotherapy with respect to the specific severe AE of musculoskeletal and connective tissue disorders (SOC).

There is a statistically significant disadvantage of pertuzumab + trastuzumab + chemotherapy with regard to the specific AEs of diarrhoea (PT), pruritus (PT), heart failure (PT), anaemia (PT), stomatitis (PT), fatigue (PT), leukopenia (PT) and metabolism and nutrition disorders (SOC).

Heart failure (serious)

In the APHINITY study, all symptomatic heart failures due to reduced ejection fraction of the left ventricle (symptomatic left ventricular systolic dysfunction) were reported as a serious AE (SAE).

Severe heart failure is a significant adverse event for patients. However, severe heart failure occurred only rarely in both treatment groups. The magnitude of the difference in absolute terms is small.

In severe heart failure, both reversible and irreversible cardiac damage can occur. The percentage of irreversible severe heart failure in the APHINITY study cannot be conclusively estimated from the available data.

The results on side effects show a disadvantage of pertuzumab + trastuzumab + chemotherapy in serious adverse events (SAEs) and severe adverse events with CTCAE grade ≥ 3. In detail, there are disadvantages in the specific AEs, including serious cardiac adverse events. In the APHINITY study, serious heart failures were statistically more common with pertuzumab + trastuzumab + chemotherapy. However, these were only observed in absolute numbers in a small percentage of patients in the APHINITY study.

In the side effects category, a relevant disadvantage of pertuzumab + trastuzumab + chemotherapy is found in the overall assessment.

<u>Cross-endpoint outcomes</u>

Subgroup results by age of patients (< 65 years, ≥ 65 years)

On the basis of the data from the dossier of the pharmaceutical company, a statistically significant effect modification by the age characteristic (< 65 years, ≥ 65 years) is shown for endpoints on symptomatology (nausea and vomiting (end of anti-HER2 therapy), loss of appetite (end of anti-HER2 therapy) and in individual endpoints on health-related quality of life (physical functioning (end of anti-HER2 therapy), role functioning (36-month follow-up)) and for side effects in the endpoint of skin and subcutaneous tissue disorders (SOC, severe AEs). The subgroup results indicate less favourable effects in these endpoints for older patients ≥ 65 years.

This effect modification is not evident in other patient individual endpoints.

These subgroup results are considered a relevant outcome of the present benefit assessment. However, these are not considered sufficient to differentiate by age in the overall assessment and to derive corresponding separate statements on the additional benefit.

Overall assessment

In the present benefit assessment, the SC fixed combination pertuzumab/trastuzumab is evaluated. In the context of the marketing authorisation of the SC fixed combination, bio-equivalence and efficacy equivalence were demonstrated in comparison to the free IV combination of pertuzumab + trastuzumab. The present assessment is therefore based on the data regarding the free combination from the APHINITY study.

Results on mortality (overall survival), morbidity, quality of life and side effects from the APHINITY study are available for the assessment of pertuzumab/ trastuzumab in combination with chemotherapy compared to the appropriate comparator therapy (trastuzumab + chemotherapy).

In the mortality endpoint category, there is a statistically significant difference in favour of pertuzumab + trastuzumab + chemotherapy. The median survival time has not yet been reached in either treatment arm. Due to the low magnitude and the questionable validity of the observed effect in the mortality endpoint category, neither an advantage nor a disadvantage of pertuzumab + trastuzumab + chemotherapy in the mortality endpoint category is determined overall against the background of the uncertainties of the study with regard to the subsequent therapies and thus, the transferability to the German healthcare context.

With regard to the results on recurrences, presented as recurrence rate and disease-free survival, a relevant advantage of pertuzumab + trastuzumab + chemotherapy over trastuzumab + chemotherapy is observed. The avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting.

Overall, neither an advantage nor a disadvantage of treatment with pertuzumab + trastuzumab + chemotherapy can be derived from the results on symptomatology.

Overall, there was no advantage or disadvantage of pertuzumab + trastuzumab + chemotherapy over trastuzumab + chemotherapy for health-related quality of life.

With regard to side effects, there is a relevant disadvantage overall. This is based on statistically significant disadvantages in serious adverse events (SAEs) and severe adverse events with CTCAE grade ≥ 3. In detail, there are disadvantages in the specific AEs, including serious cardiac adverse events. However, serious heart failures were observed in absolute numbers only in a small percentage of patients.

In the overall assessment, no advantage or disadvantage relevant to the benefit assessment can be determined with regard to overall survival. The advantage in terms of avoiding recurrences is offset by relevant negative effects in terms of side effects. In a weighted decision, the G-BA comes to the conclusion that the advantages outweigh the disadvantages.

As a result, the G-BA determined a minor additional benefit of pertuzumab/ trastuzumab in combination with chemotherapy in the adjuvant treatment of adults with HER2-positive early breast cancer at high risk of recurrence compared to trastuzumab + chemotherapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, controlled, double-blind APHINITY study.

The risk of bias at study level is rated as low.

The endpoint-specific risk of bias for the endpoints on recurrences and side effects is estimated to be low.

Thus, the reliability of data for the additional benefit determined is classified in the category "indication".

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of pertuzumab/ trastuzumab due to the expiry of the limitation of the resolution of 15 July 2021.

The combination of active ingredients pertuzumab/ trastuzumab is approved for the adjuvant treatment of adult patients with HER2-positive early 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.

In the context of the marketing authorisation of the SC fixed combination, bio-equivalence and efficacy equivalence were demonstrated in comparison to the free IV combination of pertuzumab + trastuzumab. Therefore, the assessment is based on the data regarding the free combination from the APHINITY study comparing pertuzumab + trastuzumab + chemotherapy with trastuzumab + chemotherapy.

There is a statistically significant advantage for overall survival. The median survival time has not yet been reached in either treatment arm. Neither an advantage nor a disadvantage is determined overall due to the minor extent and the questionable validity of the observed effect on overall survival, against the background of the uncertainties of the study regarding the subsequent therapies.

For recurrences, presented as recurrence rate and disease-free survival, a relevant advantage of pertuzumab + trastuzumab + chemotherapy is observed. The avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting.

In terms of symptomatology and health-related quality of life, there are neither advantages nor disadvantages overall.

For side effects, a relevant disadvantage is shown due to the statistically significant disadvantages in serious adverse events and severe adverse events (CTCAE grade ≥ 3). In detail, there are disadvantages in the specific AEs, including serious cardiac adverse events. However, serious heart failures were observed in absolute numbers only in a small percentage of patients.

In the overall assessment, no advantage or disadvantage relevant to the benefit assessment can be determined with regard to overall survival. The advantage in terms of avoiding recurrences is offset by relevant negative effects in terms of side effects. In a weighted decision, the G-BA comes to the conclusion that the advantages outweigh the disadvantages.

As a result, the G-BA determined a minor additional benefit of pertuzumab/ trastuzumab in combination with chemotherapy compared to trastuzumab + chemotherapy.

The risk of bias at study level is rated as low. With regard to the reliability of data, an indication is determined.

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 resolution is based on the information from the dossier of the pharmaceutical company.

The number estimated by the pharmaceutical company is potentially underestimated as only the number of new breast cancer cases is used for the baseline population of 2022. It cannot be ruled out that patients diagnosed before the current year meet the criteria of the present therapeutic indication in adjuvant treatment setting in the current year. In addition, patients who could be treated with neoadjuvant therapy were excluded from the outset when determining the baseline population, although adjunctive therapy also represents a possible therapeutic alternative for some of these patients.

Overall, an underestimation of the number of patients can be assumed.

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: 2 February 2023):

https://www.ema.europa.eu/en/documents/product-information/phesgo-epar-product-information_en.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.

Pertuzumab/ trastuzumab should be used by medical professionals trained in the treatment of anaphylaxis and in an environment where full resuscitation equipment is 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: 1 March 2023).

Pertuzumab/ trastuzumab and trastuzumab

According to the product information, pertuzumab/ trastuzumab should be administered for a total of one year (up to 18 cycles or until recurrence or until the occurrence of unmanageable toxicity, whichever comes first) as part of a complete treatment regimen for early stage breast cancer, regardless of the time of surgery. Treatment with pertuzumab/ trastuzumab is to be started on day 1 of the first taxane-containing cycle and should be continued even if chemotherapy is stopped.

Thus, the calculation of the annual treatment costs is based on 18 cycles. The 18th cycle starts already in the period of one year, and the application of pertuzumab/ trastuzumab takes place on day 1 of this cycle. Accordingly, the treatment with trastuzumab in the context of the appropriate comparator therapy is also based on 18 cycles, which is consistent with the information in the trastuzumab product information and corresponds to the application in the comparator arm of the APHINITY study.

Trastuzumab

The data on trastuzumab is based on the intravenous (IV) application.

Chemotherapy Regimen

The information on chemotherapy regimens is based on the doses in the APHINITY approval study.

Carboplatin

In the anthracycline-free therapy regimen, the dose is determined individually, taking into account renal function (glomerular filtration rate [GFR]). The median carboplatin dose administered per cycle in the APHINITY study is used for the present treatment costs: 649 mg in the pertuzumab arm and 660 mg in the control arm.

The information on dosages refers to applications in women, as breast cancer is relatively rare in men. The average body measurements of adult females were applied for dosages, depending on body weight (BW) or body surface area (BSA) (average body height: 1.66 m; average body weight: 68.7 kg)[3]. This results in a body surface area of 1.76 m² (calculated according to Du Bois 1916).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Pertuzumab/ trastuzumab	1 x every 21 days	18	1	18
In combination with one of the following chemotherapy regimens:				
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC), docetaxel *or* paclitaxel (q1w)				
5-fluorouracil	1 x every 21 days	3 to 4	1	3 to 4
Epirubicin	1 x every 21 days	3 to 4	1	3 to 4
Cyclophosphamide	1 x every 21 days	3 to 4	1	3 to 4
Docetaxel	1 x every 21 days	3 to 4	1	3 to 4
or				
Paclitaxel (q1w)	1 x every 7 days	12	1	12
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), docetaxel *or* paclitaxel (q1w)				
5-fluorouracil	1 x every 21 days	3 to 4	1	3 to 4
Doxorubicin	1 x every 21 days	3 to 4	1	3 to 4
Cyclophosphamide	1 x every 21 days	3 to 4	1	3 to 4
Docetaxel	1 x every 21 days	3 to 4	1	3 to 4
or				
Paclitaxel (q1w)	1 x every 7 days	12	1	12
+ doxorubicin + cyclophosphamide (AC), docetaxel *or* paclitaxel (q1w)				
Doxorubicin	1 x every 21 days	4	1	4

[3] Federal Health Reporting. Average body measurements of the population (2017), www.gbe-bund.de

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cyclophosphamide	1 x every 21 days	4	1	4
Docetaxel	1 x every 21 days	3 to 4	1	3 to 4
or				
Paclitaxel (q1w)	1 x every 7 days	12	1	12
+ epirubicin + cyclophosphamide (EC), docetaxel *or* paclitaxel (q1w)				
Epirubicin	1 x every 21 days	4	1	4
Cyclophosphamide	1 x every 21 days	4	1	4
Docetaxel	1 x every 21 days	3 to 4	1	3 to 4
or				
Paclitaxel (q1w)	1 x every 7 days	12	1	12
+ docetaxel + carboplatin				
Docetaxel	1 x every 21 days	6	1	6
Carboplatin	1 x every 21 days	6	1	6
Appropriate comparator therapy				
Trastuzumab	1 x every 21 days	18	1	18
In combination with one of the following chemotherapy regimens:				
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC), docetaxel *or* paclitaxel (q1w)				
5-fluorouracil	1 x every 21 days	3 to 4	1	3 to 4
Epirubicin	1 x every 21 days	3 to 4	1	3 to 4
Cyclophosphamide	1 x every 21 days	3 to 4	1	3 to 4
Docetaxel	1 x every 21 days	3 to 4	1	3 to 4
or				
Paclitaxel (q1w)	1 x every 7 days	12	1	12
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), docetaxel *or* paclitaxel (q1w)				
5-fluorouracil	1 x every 21 days	3 to 4	1	3 to 4
Doxorubicin	1 x every 21 days	3 to 4	1	3 to 4
Cyclophosphamide	1 x every 21 days	3 to 4	1	3 to 4
Docetaxel	1 x every 21 days	3 to 4	1	3 to 4
or				
Paclitaxel (q1w)	1 x every 7 days	12	1	12
+ doxorubicin + cyclophosphamide (AC), docetaxel *or* paclitaxel (q1w)				
Doxorubicin	1 x every 21 days	4	1	4
Cyclophosphamide	1 x every 21 days	4	1	4
Docetaxel	1 x every 21 days	3 to 4	1	3 to 4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
or				
Paclitaxel (q1w)	1 x every 7 days	12	1	12
+ epirubicin + cyclophosphamide (EC), docetaxel *or* paclitaxel (q1w)				
Epirubicin	1 x every 21 days	4	1	4
Cyclophosphamide	1 x every 21 days	4	1	4
Docetaxel	1 x every 21 days	3 to 4	1	3 to 4
or				
Paclitaxel (q1w)	1 x every 7 days	12	1	12
+ docetaxel + carboplatin				
Docetaxel	1 x every 21 days	6	1	6
Carboplatin	1 x every 21 days	6	1	6

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	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: 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	1 17	1 x 1,200 mg/ 600 mg + 17 x 600 mg/ 600 mg
In combination with one of the following chemotherapy regimens:					
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC) + docetaxel *or* paclitaxel (q1w)					
5-fluorouracil	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	1 x 1,000 mg up to 1 x 2,500 mg	3 to 4	3 x 1,000 mg up to 4 x 2,500 mg
Epirubicin	90 mg/m² - 120 mg/m²	158.4 mg - 211.2 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg up to 1 x 200 mg + 2 x 10 mg	3 to 4	3 x 100 mg + 3 x 50 mg + 3 x 10 mg up to 4 x 200 mg + 8 x 10 mg
Cyclophosphamide	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	18 x 50 mg up to 22 x 50 mg	3 to 4	54 x 50 mg up to 88 x 50 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Docetaxel	75 mg/m² - 100 mg/m²	132 mg - 176 mg	1 x 140 mg up to 1 x 140 mg + 2 x 20 mg	3 to 4	3 x 140 mg up to 4 x 140 mg + 8 x 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 x 150 mg	12	12 x 150 mg
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), docetaxel *or* paclitaxel (q1w)					
5-fluorouracil	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	1 x 1,000 mg up to 1 x 2,500 mg	3 to 4	3 x 1,000 mg up to 4 x 2,500 mg
Doxorubicin	50 mg/m²	88 mg	1 x 100 mg	3 to 4	3 x 100 mg up to 4 x 100 mg
Cyclophosphamide	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	18 x 50 mg up to 22 x 50 mg	3 to 4	54 x 50 mg up to 88 x 50 mg
Docetaxel	75 mg/m² - 100 mg/m²	132 mg - 176 mg	1 x 140 mg up to 1 x 140 mg + 2 x 20 mg	3 to 4	3 x 140 mg up to 4 x 140 mg + 8 x 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 x 150 mg	12	12 x 150 mg
+ doxorubicin + cyclophosphamide (AC), docetaxel *or* paclitaxel (q1w)					
Doxorubicin	60 mg/m²	105.6 mg	1 x 100 mg + 1 x 10 mg	4	4 x 100 mg + 4 x 10 mg
Cyclophosphamide	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	18 x 50 mg up to 22 x 50 mg	4	72 x 50 mg up to 88 x 50 mg
Docetaxel	75 mg/m² - 100 mg/m²	132 mg - 176 mg	1 x 140 mg up to 1 x 140 mg + 2 x 20 mg	3 to 4	3 x 140 mg up to 4 x 140 mg + 8 x 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 x 150 mg	12	12 x 150 mg
+ epirubicin + cyclophosphamide (EC), docetaxel *or* paclitaxel (q1w)					
Epirubicin	90 mg/m² - 120 mg/m²	158.4 mg - 211.2 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg up to 1 x 200 mg + 2 x 10 mg	4	4 x 100 mg + 4 x 50 mg+ 4 x 10 mg up to 4 x 200 mg + 8 x 10 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cyclophosphamide	500 mg/m² - 600 mg/m²	880 mg - 1056 mg	18 x 50 mg up to 22 x 50 mg	4	72 x 50 mg up to 88 x 50 mg
Docetaxel	75 mg/m² - 100 mg/m²	132 mg - 176 mg	1 x 140 mg up to 1 x 140 mg + 2 x 20 mg	3 to 4	3 x 140 mg up to 4 x 140 mg + 8 x 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 x 150 mg	12	12 x 150 mg
+ docetaxel + carboplatin					
Docetaxel	75 mg/m²	132 mg	1 x 140 mg	6	6 x 140 mg
Carboplatin	individual[4]	649 mg[5]	1 x 600 mg + 1 x 50 mg	6	6 x 600 mg + 6 x 50 mg
Appropriate comparator therapy					
Trastuzumab	Cycle 1: 8 mg/kg From cycle 2: 6 mg/kg	549.6 mg 412.2 mg	1 x 420 mg + 1 x 150 mg 1 x 420 mg	1 17	1 x 420 mg + 1 x 150 mg 17 x 420 mg
In combination with one of the following chemotherapy regimens:					
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC) + docetaxel *or* paclitaxel (q1w)					
5-fluorouracil	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	1 x 1,000 mg up to 1 x 2,500 mg	3 to 4	3 x 1,000 mg up to 4 x 2,500 mg
Epirubicin	90 mg/m² - 120 mg/m²	158.4 mg - 211.2 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg up to 1 x 200 mg + 2 x 10 mg	3 to 4	3 x 100 mg + 3 x 50 mg + 3 x 10 mg up to 4 x 200 mg + 8 x 10 mg
Cyclophosphamide	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	18 x 50 mg up to 22 x 50 mg	3 to 4	54 x 50 mg up to 88 x 50 mg
Docetaxel	75 mg/m² - 100 mg/m²	132 mg - 176 mg	1 x 140 mg up to 1 x 140 mg + 2 x 20 mg	3 to 4	3 x 140 mg up to 4 x 140 mg + 8 x 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 x 150 mg	12	12 x 150 mg
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), docetaxel *or* paclitaxel (q1w)					

[4] Taking into account the renal function (glomerular filtration rate [GFR])
[5] Median carboplatin dose administered per cycle in the APHINITY study

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
5-fluorouracil	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	1 x 1,000 mg up to 1 x 2,500 mg	3 to 4	3 x 1,000 mg up to 4 x 2,500 mg
Doxorubicin	50 mg/m²	88 mg	1 x 100 mg	3 to 4	3 x 100 mg up to 4 x 100 mg
Cyclophosphamide	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	18 x 50 mg up to 22 x 50 mg	3 to 4	54 x 50 mg up to 88 x 50 mg
Docetaxel	75 mg/m² - 100 mg/m²	132 mg - 176 mg	1 x 140 mg up to 1 x 140 mg + 2 x 20 mg	3 to 4	3 x 140 mg up to 4 x 140 mg + 8 x 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 x 150 mg	12	12 x 150 mg
+ doxorubicin + cyclophosphamide (AC), docetaxel *or* paclitaxel (q1w)					
Doxorubicin	60 mg/m²	105.6 mg	1 x 100 mg + 1 x 10 mg	4	4 x 100 mg + 4 x 10 mg
Cyclophosphamide	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	18 x 50 mg up to 22 x 50 mg	4	72 x 50 mg up to 88 x 50 mg
Docetaxel	75 mg/m² - 100 mg/m²	132 mg - 176 mg	1 x 140 mg up to 1 x 140 mg + 2 x 20 mg	3 to 4	3 x 140 mg up to 4 x 140 mg + 8 x 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 x 150 mg	12	12 x 150 mg
+ epirubicin + cyclophosphamide (EC), docetaxel *or* paclitaxel (q1w)					
Epirubicin	90 mg/m² - 120 mg/m²	158.4 mg - 211.2 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg up to 1 x 200 mg + 2 x 10 mg	4	4 x 100 mg + 4 x 50 mg+ 4 x 10 mg up to 4 x 200 mg + 8 x 10 mg
Cyclophosphamide	500 mg/m² - 600 mg/m²	880 mg - 1,056 mg	18 x 50 mg up to 22 x 50 mg	4	72 x 50 mg up to 88 x 50 mg
Docetaxel	75 mg/m² - 100 mg/m²	132 mg - 176 mg	1 x 140 mg up to 1 x 140 mg + 2 x 20 mg	3 to 4	3 x 140 mg up to 4 x 140 mg + 8 x 20 mg
or					

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 x 150 mg	12	12 x 150 mg
+ docetaxel + carboplatin					
Docetaxel	75 mg/m²	132 mg	1 x 140 mg	6	6 x 140 mg
Carboplatin	individual[6]	660 mg[7]	1 x 600 mg 2 x 50 mg	6	6 x 600 mg 12 x 50 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Trastuzumab 600 mg Pertuzumab 600 mg	1 SFI	€ 4,895.67	€ 2.00	€ 473.66	€ 4,420.01
Pertuzumab 1,200 mg Trastuzumab 600 mg	1 SFI	€ 7,617.51	€ 2.00	€ 740.14	€ 6,875.37
Carboplatin 50 mg	1 CIS	€ 34.63	€ 2.00	€ 1.11	€ 31.52
Carboplatin 600 mg	1 CIS	€ 300.81	€ 2.00	€ 13.74	€ 285.07
Cyclophosphamide 50 mg[8]	100 CTA	€ 49.75	€ 2.00	€ 0.00	€ 47.75
Docetaxel 20 mg	1 CIS	€ 112.43	€ 2.00	€ 4.80	€ 105.63
Docetaxel 140 mg	1 CIS	€ 719.30	€ 2.00	€ 33.60	€ 683.70
Doxorubicin 10 mg[8]	1 CIS	€ 40.28	€ 2.00	€ 2.29	€ 35.99
Doxorubicin 100 mg[8]	1 CIS	€ 285.75	€ 2.00	€ 0.00	€ 283.75
Epirubicin 10 mg	1 CIS	€ 39.47	€ 2.00	€ 1.34	€ 36.13
Epirubicin 50 mg	1 CIS	€ 155.41	€ 2.00	€ 6.84	€ 146.57
Epirubicin 100 mg	1 CIS	€ 300.81	€ 2.00	€ 13.74	€ 285.07
Epirubicin 10 mg	1 SFI	€ 39.47	€ 2.00	€ 1.34	€ 36.13

[6] Taking into account renal function (glomerular filtration rate [GFR])
[7] Median carboplatin dose administered per cycle in the APHINITY study
[8] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Epirubicin 200 mg	1 SFI	€ 590.32	€ 2.00	€ 27.48	€ 560.84
Fluorouracil 1,000 mg[8]	1 IIS	€ 16.64	€ 2.00	€ 0.42	€ 14.22
Fluorouracil 2500 mg[8]	1 SFI	€ 23.56	€ 2.00	€ 0.00	€ 21.56
Paclitaxel 150 mg	1 CIS	€ 428.94	€ 2.00	€ 19.82	€ 407.12
Appropriate comparator therapy					
Trastuzumab 150 mg	1 PIC	€ 798.19	€ 2.00	€ 74.69	€ 721.50
Trastuzumab 420 mg	1 PIC	€ 2,216.18	€ 2.00	€ 211.33	€ 2,002.85
Carboplatin 50 mg	1 CIS	€ 34.63	€ 2.00	€ 1.11	€ 31.52
Carboplatin 600 mg	1 CIS	€ 300.81	€ 2.00	€ 13.74	€ 285.07
Cyclophosphamide 50 mg[8]	100 CTA	€ 49.75	€ 2.00	€ 0.00	€ 47.75
Docetaxel 20 mg	1 CIS	€ 112.43	€ 2.00	€ 4.80	€ 105.63
Docetaxel 140 mg	1 CIS	€ 719.30	€ 2.00	€ 33.60	€ 683.70
Doxorubicin 10 mg[8]	1 CIS	€ 40.28	€ 2.00	€ 2.29	€ 35.99
Doxorubicin 100 mg[8]	1 CIS	€ 285.75	€ 2.00	€ 0.00	€ 283.75
Epirubicin 10 mg	1 CIS	€ 39.47	€ 2.00	€ 1.34	€ 36.13
Epirubicin 50 mg	1 CIS	€ 155.41	€ 2.00	€ 6.84	€ 146.57
Epirubicin 100 mg	1 CIS	€ 300.81	€ 2.00	€ 13.74	€ 285.07
Epirubicin 10 mg	1 SFI	€ 39.47	€ 2.00	€ 1.34	€ 36.13
Epirubicin 200 mg	1 SFI	€ 590.32	€ 2.00	€ 27.48	€ 560.84
Fluorouracil 1,000 mg[8]	1 IIS	€ 16.64	€ 2.00	€ 0.42	€ 14.22
Fluorouracil 2500 mg[8]	1 SFI	€ 23.56	€ 2.00	€ 0.00	€ 21.56
Paclitaxel 150 mg	1 CIS	€ 428.94	€ 2.00	€ 19.82	€ 407.12

Abbreviations: CIS = concentrate for the preparation of an infusion solution; IIS = injection/ infusion solution; SfI = solution for injection; PIC = powder for the preparation of an infusion solution concentrate; CTA = coated tablets

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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 the standard expenditure in the course of the treatment are not shown.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Paclitaxel (q1w)							
Dexamethasone 2 x 20 mg[8]	20 TAB 20 mg each	€ 54.05	€ 2.00	€ 0.00	€ 52.05	12	€ 82.43
	10 TAB, each 20 mg	€ 32.38	€ 2.00	€ 0.00	€ 30.38		
Dimetindene IV 1 mg/10 kg	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	12	€ 79.30
Cimetidine IV 300 mg[8]	10 AMP each 200 mg	€ 19.77	€ 2.00	€ 0.40	€ 17.37	12	€ 52.11
Abbreviations: AMP = ampoules; SFI = solution for injection; TAB = tablets							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 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 € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales 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 purchase 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 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 Pertuzumab/ Trastuzumab

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 27 September 2022, 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 5 VerfO.

By letter dated 29 September 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 combination of active ingredients pertuzumab/ trastuzumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 23 December 2022, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2023. The deadline for submitting written statements was 23 January 2023.

The oral hearing was held on 6 February 2023.

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 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 was discussed at the session of the subcommittee on 7 March 2023, and the proposed resolution was approved.

At its session on 16 March 2023, 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	31 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 February 2023	Conduct of the oral hearing
Working group Section 35a	14 February 2023 28 February 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	7 March 2023	Concluding discussion of the draft resolution
Plenum	16 March 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 March 2023

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

Prof. Hecken