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, early stage at high risk of recurrence, adjuvant)

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

Therapeutic indication of the resolution (resolution of 15.07.2021):

see 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.

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.
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.

1 General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 terms of authorisation status, the following agents are available for the adjuvant treatment of HER2 positive, early stage breast cancer at high risk of recurrence: cyclophosphamide, docetaxel, doxorubicin, epirubicin, 5-fluorouracil, methotrexate, paclitaxel, vincristine, trastuzumab, trastuzumab emtansine and pertuzumab.

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 (expires 1 October 2022)

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 adjuvant treatment 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.

Adjuvant radiotherapy has a high value in the present therapeutic indication, especially in case of a high risk of recurrence. However, radiotherapy is not part of the appropriate

comparator therapy. The use of radiotherapy as a patient-individual therapy option remains unaffected.

The active ingredient pertuzumab was evaluated within the benefit assessment framework according to Section 35a SGB V. Pertuzumab is indicated for use in combination with trastuzumab and chemotherapy for the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence. With the resolution of the G-BA of 20 December 2018, a hint of a minor additional benefit was identified for pertuzumab in the adjuvant therapy situation 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 resolution was made in particular due to outstanding data on overall survival and recurrences in the APHINITY study as of 1 October 2022. In the overall consideration of the available evidence, the active ingredient pertuzumab is determined as not being 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.

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:

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 evidence of a hint for a minor additional benefit.

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 pertuzumab + trastuzumab with the FeDeriCa study. The pharmaceutical company, therefore, derives the additional benefit independently of the dosage form. For the proof of the additional benefit of pertuzumab/trastuzumab for the adjuvant treatment of adult HER2-positive early stage breast cancer at high risk of recurrence, the pharmaceutical company, therefore, presents the results of the APHINITY study, which was also the basis of the benefit assessment of pertuzumab in free combination with trastuzumab already conducted[2]. The G-BA considers these data to be suitable and bases the present benefit assessment on them.

APHINITY is a multicentre, double-blind, randomised study comparing pertuzumab + trastuzumab + chemotherapy with placebo + trastuzumab + chemotherapy regimen. The global study, which is still ongoing and started in November 2011, enrolled adults with HER2-

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

positive early stage breast cancer. Prior to the start of the study, the primary tumours and any affected lymph nodes were completely resected surgically.

The 4805 patients included were randomised 1:1 to the pertuzumab + trastuzumab + chemotherapy arm and to the trastuzumab + placebo + chemotherapy arm. Regarding chemotherapy, different chemotherapy regimens were available in the study, both with and without anthracyclines. The principal investigator made selection prior to randomisation. 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).

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

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

This benefit assessment is based on the results of the a priori planned data cut-offs of 19.12.2016 and 19.06.2019. The final overall survival analysis will occur when 640 deaths have occurred (approximately 9 to 10 years after the last patient was randomised).

Extent and probability of the additional benefit

Mortality

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

For the endpoint overall survival, there was no statistically significant difference between the treatment groups. No additional benefit is identified for the endpoint overall survival.

The final analysis on overall survival from the currently ongoing study is still pending.

On the validity of the endpoint DFS as a surrogate for overall survival

In its dossier for benefit assessment, the pharmaceutical company presents a surrogate validation SV2 on the validity of the endpoint *disease-free survival* (DFS) as a surrogate for overall survival in patients with HER2-positive early stage breast cancer receiving adjuvant therapy with anti-HER2 antibodies.

In its assessment, IQWiG concludes that the submitted surrogate validation SV2 (based on Saad et al.[3]) is not suitable for investigating the validity of DFS as a surrogate for overall survival in the present situation. Thus, the inclusion criteria of the validation study are not appropriate, as the comparator therapy defined there systematically excludes anti-HER2 therapies in approved doses and treatment duration. Furthermore, the pharmaceutical company's information retrieval is not appropriate as it is based on the inappropriate inclusion criteria of the Saad 2019 study and consequently is not suitable to identify relevant studies in the present research question.

Moreover, the surrogate validation study submitted by the pharmaceutical entrepreneur in the dossier corresponds to the analysis submitted by the pharmaceutical company in a

[3] Saad et al. Disease-free survival as a surrogate for overall survival in patients with HER2-positive, early breast cancer in trials of adjuvant trastuzumab for up to 1 year: a systematic review and meta-analysis. Lancet Oncol 2019; 20(3): 361-370

previous procedure in the same therapeutic indication (citation Trastuzumab emtansine 2020-01-15-D-498). The G-BA had already assessed these as unsuitable in the procedure mentioned above (citation trastuzumab emtansine 2020-01-15-D-498).

Thus, no conclusions can be drawn regarding the validity of DFS as a surrogate endpoint for the endpoint overall survival. The endpoint DFS is included in the present evaluation as a separate patient-individual endpoint.

Morbidity

Recurrences (event rate and disease-free survival)

The patients in the present therapeutic indication are treated with a curative therapy approach: adjuvant therapy after complete resection of the primary tumours and possibly affected lymph nodes. The 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.

The combined endpoint recurrences include the following individual components:

- 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)
- Death from any cause

The endpoint recurrence, operationalised as recurrence rate, describes the proportion of individuals with a recurrence event or death at the corresponding data cut-off (event rate). In the endpoint DFS, the time to the event (recurrence or death) is also considered (time-to-event analysis).

The endpoints recurrence (event rate) and disease-free survival (DFS) are used for the present evaluation.

Recurrences (event rate)

There is a statistically significant difference for the benefit of pertuzumab + trastuzumab + chemotherapy compared to placebo + trastuzumab + chemotherapy for the recurrence rate. The endpoint recurrence rate includes the same individual components and thus the same recurrence events as well as deaths before recurrence events as another component as the endpoint DFS.

Disease-free survival (DFS)

The time-to-event analysis shows a statistically significant positive effect for pertuzumab + trastuzumab + chemotherapy.

When considering both endpoints, a positive effect, quantitatively small, is observed with regard to the avoidance of recurrences for pertuzumab + trastuzumab + chemotherapy.

Symptomatology

The functional scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module EORTC QLQ-BR23 were used in the APHINITY study to assess health-related quality of life.

For the present 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 nausea and vomiting and loss of appetite, there were statistically significant disadvantages of pertuzumab + trastuzumab + chemotherapy for the endpoints nausea and vomiting and loss of appetite compared with trastuzumab + trastuzumab + chemotherapy at the end of anti-HER2 therapy. At the 36-month follow-up, these endpoints no longer show statistically significant differences.

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

For the other presented endpoints, no statistically significant difference was detected between the study arms.

In the overall analysis of the endpoints on symptomatology, statistically significant disadvantages of treatment with pertuzumab + trastuzumab + chemotherapy were present only directly to the end of anti-HER2 therapy and only in individual endpoints. However, all of these adverse effects are no longer evident at the 36-month follow-up; there is even a statistically significant advantage for the endpoint diarrhoea. In terms of symptomatology, neither an advantage nor a disadvantage can be determined for pertuzumab + trastuzumab + chemotherapy treatment.

Quality of life

The functional scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific supplementary module QLQ-BR23 were used in the APHINITY study to assess health-related quality of life.

For the present 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 function, there was a statistically significant difference in benefit of pertuzumab + trastuzumab + chemotherapy at 36-month follow-up. The effect is small in quantitative terms.

Regarding the other endpoints, there is no statistically significant difference.

Overall, neither an advantage nor a disadvantage of treatment with pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy is found for health-related quality of life.

Side effects

Adverse events (AEs)

Nearly every person in the APHINITY study experienced an AE at least once, both when treated with pertuzumab + trastuzumab + chemotherapy and when treated with trastuzumab + chemotherapy.

Serious adverse events (SAEs)

There was a statistically significant effect to the disadvantage of pertuzumab + trastuzumab + chemotherapy for serious adverse events.

Severe AEs (CTCAE grade 3 or 4)

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

In the subgroup analysis by region (with the 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 AE

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

Specific AE

The selection of specific AEs was done according to the methodology of the IQWiG using events that occurred in the study based on frequency and differences between treatment arms and taking into account patient relevance.

There was a statistically significant advantage for pertuzumab + trastuzumab + chemotherapy over trastuzumab + chemotherapy concerning the specific severe AE (CTCAE grade 3 or 4) musculoskeletal and connective tissue disorders (SOC).

In contrast, pertuzumab + trastuzumab + chemotherapy showed a statistically significant disadvantage concerning the specific AEs diarrhoea (PT), pruritus (PT), cardiac insufficiency (PT,) as well as the specific severe AE (CTCAE grade 3 or 4) anaemia (PT), diarrhoea (PT), stomatitis (PT), fatigue (PT), leukopenia (PT), and metabolism and nutrition disorders (SOC).

Cardiac insufficiency (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 cardiac insufficiency is a significant adverse event for affected patients. It is a rare event in both treatment groups regarding the number of serious heart failures in the APHINITY study. The magnitude of the difference in absolute terms is small.

Severe cardiac insufficiency can be both a reversible and irreversible cardiac injury. The proportion of irreversible severe heart failure in the APHINITY study cannot be conclusively assessed based on the available data.

In summary, there is a disadvantage for pertuzumab + trastuzumab + chemotherapy due to an increase in serious adverse events (SAE) and severe adverse events with CTCAE grade ≥ 3. In detail, the specific AEs show a disadvantage in terms of serious cardiac side effects, among others. Cardiotoxicity is generally of high importance in treatment with anthracyclines and the anti-HER2 antibodies pertuzumab and trastuzumab. The present benefit assessment shows a statistically significant increase in severe heart failure during treatment with pertuzumab + trastuzumab + chemotherapy. However, this disadvantage affects only a small proportion of patients in absolute terms. A significant disadvantage for pertuzumab + trastuzumab + chemotherapy is found in the overall consideration of side effects.

Cross-endpoint outcomes:

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

In individual endpoints on symptomatology (nausea and vomiting (end of anti-HER2 therapy), loss of appetite (end of anti-HER2 therapy) as well as in individual endpoints on health-related quality of life (physical functioning (end of anti-HER2 therapy), role function (36-month follow-up) and in side effects in the endpoint skin and subcutaneous tissue disorders (SOC, severe AE), a statistically significant effect modification is shown in the subgroup analysis for the characteristic age (< 65 years, ≥ 65 years). 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.

A separate statement on the additional benefit based on the subgroup analyses for the characteristic age (< 65 years, ≥ 65 years) is not made by the G-BA in the present case. A rigid age limit for the separate derivation of an additional benefit (persons < 65 years or ≥ 65 years) appears problematic considering the reality of care. Thus, in addition to the age according to the calendar, the general condition and the existing comorbidity, among other things, are also taken into account in the doctor's treatment decision. This view was also expressed in the opinions of medical experts in the present proceeding.

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. The present assessment is therefore based on the free combination data from the APHINITY study.

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

In the endpoint category mortality, the present results for the endpoint overall survival show no statistically significant difference between the study arms. The median survival has not yet been reached due to the low number of events. The final analysis on the endpoint overall survival is pending. For the endpoint overall survival, an additional benefit is therefore not proven.

For recurrences that occurred, presented as recurrence rate and DFS, there were statistically significantly fewer recurrences for pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy. The magnitude of this effect is rated as a relevant but no more than a moderate improvement. The avoidance of recurrences is an essential therapeutic goal in the present curative therapy situation.

With regard to the symptomatology assessed in the study, neither an advantage nor a disadvantage can be determined overall from treatment with pertuzumab + trastuzumab + chemotherapy.

With regard to patient-reported health-related quality of life, there was a moderate benefit in the endpoint emotional function. This result on health-related quality of life supports the result on the overall assessment.

There was no statistically significant difference between the treatment arms for the endpoint discontinuation due to AE in the side effects. For serious adverse events (SAE) and severe

adverse events (CTCAE grade ≥ 3), there is a disadvantage of treatment with pertuzumab + trastuzumab + chemotherapy. In detail, a statistically significant increase in serious cardiac insufficiencies is shown for the cardiac side effects that are significant in the present therapeutic indication. However, this disadvantage affects only a small proportion of patients in absolute terms. A significant disadvantage for pertuzumab + trastuzumab + chemotherapy is found in the overall consideration of side effects.

In the overall view, the particularly relevant positive effect in the present adjuvant therapy situation with regard to the avoidance of recurrences, however only to a moderate extent, is offset by the significant disadvantages with regard to side effects, in particular the serious side effects. The significant disadvantages in terms of side effects are weighted against the background of the present curative therapy claim.

In a weighing decision, the G-BA, therefore, comes to the conclusion that the advantages outweigh the disadvantages. Thus, it is concluded that there is a minor additional benefit for pertuzumab/trastuzumab in combination chemotherapy compared with trastuzumab + chemotherapy in the adjuvant treatment of adults with HER2-positive early stage breast cancer at high risk of recurrence.

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 the study level is rated as low. Except for the endpoints on patient-reported symptomatology and health-related quality of life, the endpoint-specific risk of bias is estimated to be low. The risk of bias is considered high for the endpoints collected via the symptom and functional scales of the EORTC QLQ-C30 and -BR23 questionnaires. This is due to a high proportion of over 10% of patients in the relevant subpopulation who were not included in the analysis.

The above-mentioned weighing decision for the determination of the additional benefit is based on quantitatively small differences in the extent of the positive and negative therapy effects. This results in a relevant uncertainty with regard to the reliability of data.

The available results, especially on overall survival and recurrences, are based on small numbers of events and are therefore limited in their significance. Further planned interim analyses, as well as the final analysis on overall survival from the currently ongoing APHINITY study, are still pending.

Thus, despite the overall low risk of bias at the study and outcome level, the reliability of the additional benefit identified data is classified as hint.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the resolution's validity period on the present benefit assessment of pertuzumab/trastuzumab finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a paragraph 1 SGB V.

The present overall survival and recurrence results are based on the second data cut-off as of 19.06.2019 of the APHINITY study. Follow-up of overall survival and recurrences is planned in the APHINITY trial until 10 years after randomisation. Another planned interim analysis is scheduled approximately 5 years after the primary analysis.

Since further clinical data from the APHINITY study are expected, which may be relevant for evaluating the benefits of the medicinal product, it is justified to limit the validity of the present resolution.

Conditions of the limitation:

For the renewed benefit assessment of pertuzumab/trastuzumab after the expiry of the deadline, the results on all patient-relevant endpoints from the APHINITY study, in particular on overall survival and recurrences, are to be presented in the dossier at the planned data cut-off approximately 5 years after the primary analysis.

For this purpose, the G-BA considers a limitation for the resolution until 1 October 2022 to be appropriate.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product pertuzumab/ trastuzumab recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of pertuzumab/trastuzumab in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). The possibility that a benefit assessment for the medicinal product pertuzumab/trastuzumab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.5 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 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-BAas as an appropriate comparator therapy.

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. Therefore, this assessment is based on the free combination data from the APHINITY study comparing pertuzumab + trastuzumab + chemotherapy with trastuzumab + chemotherapy.

An additional benefit is not proven for the endpoint overall survival.

For recurrences, presented as recurrence rate and DFS, there were statistically significantly fewer recurrences for pertuzumab + trastuzumab + chemotherapy. The avoidance of recurrences is an essential therapeutic goal in the present curative therapy situation.

In terms of symptomatology and health-related quality of life, neither an advantage nor a disadvantage between the treatments can be identified overall.

With regard to side effects, there is a significant disadvantage for pertuzumab + trastuzumab + chemotherapy. This disadvantage is reflected in the increase in serious adverse events as

well as severe adverse events with CTCAE grade ≥ 3. In detail, a statistically significant increase in serious cardiac insufficiencies is shown for the cardiac side effects that are significant in the present therapeutic indication. However, this disadvantage affects only a small proportion of patients in absolute terms.

In the overall view, the particularly relevant positive effect in the present adjuvant therapy situation regarding the avoidance of recurrences, however, only to a moderate extent, contrasts with the significant disadvantages concerning side effects, particularly concerning serious side effects.

In a weighing decision, the G-BA comes to the conclusion that the advantages outweigh the disadvantages. It is concluded that there is minor additional benefit for s.c. fixed combination pertuzumab/trastuzumab in combination with chemotherapy compared to trastuzumab in combination with chemotherapy in the adjuvant treatment of adult patients with HER2-positive early stage breast cancer at high risk of recurrence.

The risk of bias at the study and endpoint level, except for patient-reported endpoints, is considered low. The positive and negative treatment effects are based on quantitatively small differences in the magnitude of these effects. This results in a relevant uncertainty concerning the reliability of data, which is therefore classified as a hint.

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

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 2021. It cannot be ruled out that patients diagnosed before the current year meet the criteria for the use of pertuzumab in adjuvant therapy in the current year defined in the therapeutic indication.

In addition, neoadjuvant-treated patients were excluded from the outset when determining the baseline population. However, according to the therapy recommendations in guidelines, it cannot be ruled out that additional adjuvant treatment may also be indicated after neoadjuvant treatment.

The finding that the number of patients is potentially underestimated applies to the assumption that partially existing uncertainties do not outweigh the underestimation.

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).

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. 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 (i.v.) 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. 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.[4]

Treatment duration:

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

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

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

<u>Consumption:</u>

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	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 - 600 mg/m²	880 - 1,056 mg	1 x 1,000 mg to 2 x 1,000 mg	3 to 4	3 x 1,000 mg to 8 x 1,000 mg
Epirubicin	90 - 120 mg/m²	158.4 - 211.2 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg to	3 to 4	3 x 100 mg + 3 x 50 mg + 3 x 10 mg to

			1 x 200 mg + 1 x 20 mg		4 x 200 mg + 4 x 20 mg
Cyclophosphamide	500 - 600 mg/m²	880 - 1,056 mg	18 x 50 mg to 22 x 50 mg	3 to 4	54 x 50 mg to 88 x 50 mg
Docetaxel	75 - 100 mg/m²	132 - 176 mg	1 x 140 mg to 1 x 160 mg + 1 x 20 mg	3 to 4	3 x 140 mg to 4 x 160 mg + 4 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 - 600 mg/m²	880 - 1,056 mg	1 x 1,000 mg to 2 x 1,000 mg	3 to 4	3 x 1,000 mg to 8 x 1,000 mg
Doxorubicin	50 mg/m²	88 mg	1 x 100 mg	3 to 4	3 x 100 mg to 4 x 100 mg
Cyclophosphamide	500 - 600 mg/m²	880 - 1,056 mg	18 x 50 mg to 22 x 50 mg	3 to 4	54 x 50 mg to 88 x 50 mg
Docetaxel	75 - 100 mg/m²	132 - 176 mg	1 x 140 mg to 1 x 160 mg 1 x 20 mg	3 to 4	3 x 140 mg to 4 x 160 mg 4 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 - 600 mg/m²	880 - 1,056 mg	18 x 50 mg to 22 x 50 mg	4	72 x 50 mg to 88 x 50 mg
Docetaxel	75 - 100 mg/m²	132 - 176 mg	1 x 140 mg to 1 x 160 mg 1 x 20 mg	3 to 4	3 x 140 mg to 4 x 160 mg 4 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 - 120 mg/m²	158.4 - 211.2 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg to 1 x 200 mg + 1 x 20 mg	4	4 x 100 mg + 4 x 50 mg+ 4 x 10 mg to 4 x 200 mg + 4 x 20 mg

Cyclophosphamide	500 - 600 mg/m²	880 - 1,056 mg	18 x 50 mg to 22 x 50 mg	4	72 x 50 mg to 88 x 50 mg
Docetaxel	75 - 100 mg/m²	132 - 176 mg	1 x 140 mg to 1 x 160 mg 1 x 20 mg	3 to 4	3 x 140 mg to 4 x 160 mg 4 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[5]	649 mg[6]	1 x 600 mg 1 x 50 mg	6	6 x 600 mg 6 x 50 mg
Appropriate comparator therapy					
Trastuzumab	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 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 - 600 mg/m²	880 - 1,056 mg	1 x 1,000 mg to 2 x 1,000 mg	3 to 4	3 x 1,000 mg to 8 x 1,000 mg
Epirubicin	90 - 120 mg/m²	158.4 - 211.2 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg to 1 x 200 mg + 1 x 20 mg	3 to 4	3 x 100 mg + 3 x 50 mg + 3 x 10 mg to 4 x 200 mg + 4 x 20 mg
Cyclophosphamide	500 - 600 mg/m²	880 - 1,056 mg	18 x 50 mg to 22 x 50 mg	3 to 4	54 x 50 mg to 88 x 50 mg
Docetaxel	75 - 100 mg/m²	132 - 176 mg	1 x 140 mg to 1 x 160 mg 1 x 20 mg	3 to 4	3 x 140 mg to 4 x 160 mg 4 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 - 600 mg/m²	880 - 1,056 mg	1 x 1,000 mg to 2 x 1,000 mg	3 to 4	3 x 1,000 mg to 8 x 1,000 mg

[5] taking into account the kidney function (glomerular filtration rate [GFR])
[6] median carboplatin dose administered per cycle in the APHINITY study

Doxorubicin	50 mg/m²	88 mg	1 x 100 mg	3 to 4	3 x 100 mg to 4 x 100 mg
Cyclophosphamide	500 - 600 mg/m²	880 - 1,056 mg	18 x 50 mg to 22 x 50 mg	3 to 4	54 x 50 mg to 88 x 50 mg
Docetaxel	75 - 100 mg/m²	132 - 176 mg	1 x 140 mg to 1 x 160 mg 1 x 20 mg	3 to 4	3 x 140 mg to 4 x 160 mg 4 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 - 600 mg/m²	880 - 1,056 mg	18 x 50 mg to 22 x 50 mg	4	72 x 50 mg to 88 x 50 mg
Docetaxel	75 - 100 mg/m²	132 - 176 mg	1 x 140 mg to 1 x 160 mg 1 x 20 mg	3 to 4	3 x 140 mg to 4 x 160 mg 4 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 - 120 mg/m²	158.4 - 211.2 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg to 1 x 200 mg + 1 x 20 mg	4	4 x 100 mg + 4 x 50 mg+ 4 x 10 mg to 4 x 200 mg + 4 x 20 mg
Cyclophosphamide	500 - 600 mg/m²	880 - 1,056 mg	18 x 50 mg to 22 x 50 mg	4	72 x 50 mg to 88 x 50 mg
Docetaxel	75 - 100 mg/m²	132 - 176 mg	1 x 140 mg to 1 x 160 mg 1 x 20 mg	3 to 4	3 x 140 mg to 4 x 160 mg 4 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[7]	660 mg[8]	1 x 600 mg	6	6 x 600 mg

[7] taking into account renal function (glomerular filtration rate [GFR])
[8] median carboplatin dose administered per cycle in the APHINITY study

			2 x 50 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. I 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 § 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	€ 5,385.83	€ 1.77	€ 304.31	€ 5,079.75
Pertuzumab 1,200 mg Trastuzumab 600 mg	1 SFI	€ 8,107.65	€ 1.77	€ 459.75	€ 7,646.13
Carboplatin 50 mg	1 CIS	€ 34.38	€ 1.77	€ 1.11	€ 31.50
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Cyclophosphamide 50 mg[9]	100 CTA	€ 49.52	€ 1.77	€ 0.00	€ 47.75
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
Doxorubicin 10 mg[9]	1 CIS	€ 40.04	€ 1.77	€ 2.29	€ 35.98
Doxorubicin 100 mg[9]	1 CIS	€ 285.52	€ 1.77	€ 0.00	€ 283.75
Epirubicin 10 mg	1 CIS	€ 39.23	€ 1.77	€ 1.34	€ 36.12
Epirubicin 100 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Epirubicin 20 mg	1 SFI	€ 72.38	€ 1.77	€ 2.91	€ 67.70
Epirubicin 200 mg	1 SFI	€ 591.99	€ 1.77	€ 27.57	€ 562.65
Epirubicin 50 mg	1 CIS	€ 155.18	€ 1.77	€ 6.84	€ 146.57
Fluorouracil 1,000 mg[9]	5 SFI	€ 37.18	€ 1.77	€ 2.07	€ 33.34
Paclitaxel 100 mg	1 CIS	€ 289.19	€ 1.77	€ 13.20	€ 274.22
Paclitaxel 150 mg	1 CIS	€ 450.59	€ 1.77	€ 20.86	€ 427.96
Paclitaxel 30 mg	1 CIS	€ 115.51	€ 1.77	€ 4.96	€ 108.78
Paclitaxel 300 mg	1 CIS	€ 891.00	€ 1.77	€ 41.76	€ 847.47

[9]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
Paclitaxel 300 mg	1 CIS	€ 889.74	€ 1.77	€ 0.00	€ 887.97
Appropriate comparator therapy					
Trastuzumab 150 mg	1 PIC	€ 786.79	€ 1.77	€ 42.95	€ 742.07
Trastuzumab 420 mg	1 PIC	€ 2,163.13	€ 1.77	€ 120.26	€ 2,041.10
Carboplatin 50 mg	1 CIS	€ 34.38	€ 1.77	€ 1.11	€ 31.50
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Cyclophosphamide 50 mg[9]	100 CTA	€ 49.52	€ 1.77	€ 0.00	€ 47.75
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
Doxorubicin 10 mg[9]	1 CIS	€ 40.04	€ 1.77	€ 2.29	€ 35.98
Doxorubicin 100 mg[9]	1 CIS	€ 285.52	€ 1.77	€ 0.00	€ 283.75
Epirubicin 10 mg	1 CIS	€ 39.23	€ 1.77	€ 1.34	€ 36.12
Epirubicin 100 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Epirubicin 20 mg	1 SFI	€ 72.38	€ 1.77	€ 2.91	€ 67.70
Epirubicin 200 mg	1 SFI	€ 591.99	€ 1.77	€ 27.57	€ 562.65
Epirubicin 50 mg	1 CIS	€ 155.18	€ 1.77	€ 6.84	€ 146.57
Fluorouracil 1,000 mg[9]	5 SFI	€ 37.18	€ 1.77	€ 2.07	€ 33.34
Paclitaxel 100 mg	1 CIS	€ 289.19	€ 1.77	€ 13.20	€ 274.22
Paclitaxel 150 mg	1 CIS	€ 450.59	€ 1.77	€ 20.86	€ 427.96
Paclitaxel 30 mg	1 CIS	€ 115.51	€ 1.77	€ 4.96	€ 108.78
Paclitaxel 300 mg	1 CIS	€ 891.00	€ 1.77	€ 41.76	€ 847.47
Paclitaxel 300 mg	1 CIS	€ 889.74	€ 1.77	€ 0.00	€ 887.97
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIC = powder for the preparation of an infusion solution concentrate; CTA = coated tablets					

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.

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 (q1w)							
Dexamethasone 2 x 20 mg[10]	20 TAB 20 mg each	€ 53.81	€ 1.77	€ 0.00	€ 52.04	12	€ 82.41
	10 TAB à 20 mg	€ 32.14	€ 1.77	€ 0.00	€ 30.37		
Dimetindene i.v. 1 mg/10 kg	5 SFI each 4 mg	€ 18.62	€ 1.77	€ 1.92	€ 14.93	12	€ 74.65
Cimetidine i.v. 300 mg[10]	10 AMP each 200 mg	€ 21.55	€ 1.77	€ 0.00	€ 19.78	12	€ 59.34
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 only approximates 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