Justification

Gemeinsamer Bundesausschuss

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

of 20 December 2018

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 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 on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

On 31 May 2018, pertuzumab (Perjeta®) received marketing authorisation for a new therapeutic indication:

“Perjeta is indicated for use in combination with trastuzumab and chemotherapy in the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence (see Section 5.1)”

On 20 June 2018, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pertuzumab with the new therapeutic indication in due time (i.e. within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 1 October 2018, 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 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 written

statements presented on this in the written and oral hearing procedure as well as the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative) according to 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 set aside in the benefit assessment of pertuzumab.

In light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at 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 (Perjeta®) in accordance with the product information

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for the adjuvant treatment of patients with HER2-positive early breast cancer is:

- a therapy scheme containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, 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 according to 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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

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

On 1.

In terms of authorisation status, the active ingredients, the active ingredients cyclophosphamide, docetaxel, doxorubicin, epirubicin, 5-fluorouracil, methotrexate, paclitaxel, vincristine, and trastuzumab are available for the adjuvant therapy of HER2-positive breast cancer.

The marketing authorisation of trastuzumab covers its use in combination with docetaxel and carboplatin for adjuvant chemotherapy. In other constellations, carboplatin is not approved in the present therapeutic indication.

On 2.

Non-medicinal treatment options were not taken into consideration.

On 3.

There are no relevant resolutions of the G-BA on medicinal products or non-medicinal treatments in the therapeutic indication concerned.

On 4.

The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines and systematic reviews of clinical studies.

Both national and international guidelines for the adjuvant treatment of HER2-positive early breast cancer unanimously recommend therapy with trastuzumab directed against HER2. Trastuzumab must be integrated into a chemotherapy regime that includes a taxane (paclitaxel or docetaxel) and, if necessary, an anthracycline (doxorubicin or epirubicin). Trastuzumab should be administered over a period of one year.

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

In determining the appropriate comparator therapy, medicinal products with explicit marketing authorisation for the treatment of hormone receptor-positive breast carcinoma 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 contract.

2.1.3 Extent and probability of the additional benefit

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

For pertuzumab in combination with trastuzumab and chemotherapy for the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence, there is a hint for a minor additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company uses the results of the APHINITY pivotal study for the present new therapeutic indication of pertuzumab in the dossier. This is a 2-arm, randomised, double-blind, controlled Phase 3 study comparing pertuzumab + trastuzumab + chemotherapy with trastuzumab + chemotherapy.

With regard to chemotherapy, various chemotherapy regimens – both with and without anthracyclines – were available in the study. Selection was done by the investigator before randomisation. The comparator therapy used in the control arm of the study corresponds to the appropriate comparator therapy: a therapy scheme containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin).

A total of 4,805 adult patients with early HER2-positive breast cancer were included in the study. Before the start of study, the primary tumours and any affected lymph nodes were completely resected surgically. Within 56 days after surgery, patients were randomised to one of the two treatment arms at a ratio of 1:1.

According to the approved therapeutic indication: of pertuzumab, a sub-population is used for the assessment: Patients at high risk of recurrence; defined as nodal-positive or hormone receptor-negative disease (approx. 75% of the study population). Nodal status and hormone receptor status were stratification factors at randomisation. The pharmaceutical company presents the study results for this sub-population in the dossier.

The ongoing study began in November 2011 and is being conducted in 548 centres in 42 countries in North and South America, Europe, South Africa, and Asia.

The present benefit assessment is based on the results of the a priori planned primary data cut-off of 19 December 2016. Further interim analyses on overall survival are planned approx. 2.5 and 5 years after the primary analysis. The final analysis of overall survival will take place when 640 deaths have occurred (approx. 9 to 10 years after the last patient was randomised).

Extent and probability of the additional benefit

Mortality

Overall survival

For the endpoint overall survival, there was no statistically significant difference between the treatment groups (hazard ratio: 0.89, confidence interval: 0.65; 1.23, p value: 0.486). At the present data cut-off, the median survival time in both treatment groups has not been reached with an overall low number of events: 4.0% vs 4.4% deaths in the relevant sub-population of the study.

Further planned interim analyses and the final analysis of overall survival data from the ongoing study have yet to be completed.

The validity of the DFS endpoint as a surrogate for overall survival:

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

In its assessment, the IQWiG concludes that the validation study submitted is suitable to investigate the validity of DFS as a surrogate for overall survival in patients with HER2-positive early breast cancer receiving adjuvant therapy with anti-HER2 antibodies. The validation results in a mean correlation of the effects of both endpoints. The effect estimates for the endpoint DFS can thus be compared with the calculated STE values when considering future studies.

However, in the APHINITY study, the effect on DFS in this case is not large enough to be able to reliably assume that this will result in a positive effect on overall survival for the patients. Thus, the effect for the endpoint DFS is not large enough to allow a statement on overall survival.

The endpoint "disease-free survival (DFS)" is included in the present assessment as an independent patient-relevant endpoint (see following section).

Morbidity

Recurrences/disease-free survival (DFS)

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. Nevertheless, tumour cells can remain and cause a recurrence in the further course. A recurrence means that the attempt to cure the disease with the curative therapy approach was not successful. The occurrence of a recurrence is patient-relevant.

In the APHINITY study, various endpoints were surveyed. In different compositions of individual components, these consider the complex "recurrence of the disease" operationalised as the period between randomisation and the first occurrence of a recurrence event.

For the present assessment, the endpoints "recurrences (event rate)" and "disease-free survival (DFS)" are used. These include the following individual components:

- Ipsilateral invasive local breast cancer recurrence
- Ipsilateral invasive regional breast cancer recurrence
- Remote recurrence
- Contralateral invasive breast cancer
- Secondary primary carcinoma (not breast cancer)

- DCIS[2] (ipsilateral or contralateral)
- Death of any cause

While the endpoint “recurrences (event rate)” considers the proportion of patients with a recurrence event or death as the respective first event at the respective data cut-off of the study, the endpoint “disease-free survival (DFS)” also makes it possible to consider the times of the recurrence events and deaths.

Disease-free survival (DFS)

The time-to-event analysis shows a statistically significant positive effect for pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy (hazard ratio: HR: 0.78 [0.64; 0.96], p value 0.019). At the present data cut-off, the median time to a recurrence event has not been reached in either of the treatment groups.

Recurrences (event rate)

Also for the endpoint “recurrences (event rate)”, a statistically significant positive effect of comparable magnitude is shown for pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy: 166 patients (9.2%) vs 211 patients (11.6%) with a recurrence event (risk ratio: 0.79 [0.65; 0.96], p value: 0.018). The absolute difference is low: −2.4%. The recurrence rate endpoint comprises the same individual components and thus the same recurrence events and deaths before recurrence event as other components, such as the “DFS” endpoint.

In the consideration of both endpoints, a positive effect of pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy with regard to the avoidance of recurrences is determined; however, the quantitative extent of this is low.

Symptomatology

In the APHINITY study, the symptomatology was reported by the patients surveyed using the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. In each case, the proportion of patients with a deterioration of ≥ 10 points at 2 different time points is considered: End of anti-HER2 therapy and 36-month follow-up.

In the treatment group with pertuzumab + trastuzumab + chemotherapy, there are statistically significant disadvantages in the endpoints “fatigue”, “loss of appetite” and “symptoms in the breast area” 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”, there was initially a statistically significant disadvantage at the end of anti-HER2 therapy; however, at the time of the 36-month follow-up, there was a statistically significant advantage, albeit only to a small extent.

In the other endpoints on symptomatology “nausea and vomiting”, “pain”, “dyspnoea”, “insomnia”, “constipation”, “side effects of systemic therapy”, “symptoms in the arm area”, and “burden of hair loss”, there is no statistically significant difference between the treatment groups.

In the overall consideration of the endpoints on symptomatology, statistically significant disadvantages of treatment with pertuzumab + trastuzumab + chemotherapy are present only directly at the end of anti-HER2 therapy and only in individual endpoints. However, all these disadvantageous effects are no longer evident at the 36-month follow-up; there is even a statistically significant advantage for the endpoint diarrhoea.

Therefore, neither an advantage nor a disadvantage of treatment with pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy can be determined in terms of symptomatology

[2] Ductal carcinoma in situ

Quality of life

In the APHINITY study, health-related quality of life was reported by the patients and surveyed using the functional scales as well as the global health status scale of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. In each case, the proportion of patients with a deterioration of ≥ 10 points at 2 different time points is considered: End of anti-HER2 therapy and 36-month follow-up.

For the endpoint “emotional functioning”, there is a statistically significant advantage in the treatment group with pertuzumab + trastuzumab + chemotherapy at the 36-month follow-up. The quantitative magnitude of the effect is low.

There is no statistically significant difference in the other endpoints “global health status”, “physical functioning”, “role functioning”, “cognitive functioning”, “body image”, “sexual activity”, and “enjoyment of sex”.

With respect to health-related quality of life, there is neither an advantage nor a disadvantage of treatment with pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy.

Side effects

Total adverse events (AE)

Almost every patient in the APHINITY study experienced an adverse event (AE) at least once, both during treatment with pertuzumab + trastuzumab + chemotherapy and during treatment with trastuzumab + chemotherapy. The results for the endpoint “total adverse events” are presented additionally.

Serious AE

In the treatment group with pertuzumab + trastuzumab + chemotherapy, statistically significantly more patients were affected by serious adverse events (SAE).

Severe AE (CTCAE grade ≥ 3)

Adverse events classified as “severe adverse events” according to the CTCAE classification (CTCAE grade ≥ 3) occurred statistically significantly more frequently during treatment with pertuzumab + trastuzumab + chemotherapy.

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

Therapy discontinuation because of AE

There was no statistically significant difference between the treatment groups for therapy discontinuations because of AE.

Specific AE

For the benefit assessment, individual adverse events considered relevant, classified according to MedDRA term SOC (system organ class) and PT (preferred term), are used. According to the methodology of the IQWiG, the selection is made using the events that occurred in the relevant study based on the frequency and differences between the treatment arms and taking into account patient relevance. On the other hand, specific AE can be selected if they are of particular importance for the clinical presentation of the disease or are relevant for the active ingredients used in the study. Based on this methodology, the IQWiG selected the following specific AE:

Cardiac insufficiency (serious)

In the APHINITY study, all symptomatic cardiac insufficiencies that is due to reduced ejection fraction of the left ventricle *(symptomatic left ventricular systolic dysfunction)* was reported as a serious AE (SAE).

A serious cardiac insufficiency occurred statistically significantly more often in the treatment group with pertuzumab + trastuzumab + chemotherapy than in the treatment group with trastuzumab + chemotherapy. Serious cardiac insufficiency is a significant adverse event for the patients affected. In terms of the number of serious cardiac insufficiencies in the APHINITY study, it is a rare event in both treatment groups. In absolute terms, the extent of the difference is minor.
Serious cardiac insufficiency can be both reversible and irreversible cardiac damage. The proportion of irreversible serious cardiac insufficiencies in the APHINITY study cannot be conclusively assessed based on the data available.

Diarrhoea (serious and non-serious)

Serious and non-serious diarrhoea occurred statistically significantly more often in the treatment group with pertuzumab + trastuzumab + chemotherapy than in the treatment group with trastuzumab + chemotherapy. In particular, the difference in serious diarrhoea is patient-relevant. However, this adverse event is usually temporary and basically treatable. This view was also expressed in the written statements of medical experts in the present procedure.

Metabolism and nutrition disorders (serious)

A serious metabolism and nutrition disorder occurred statistically significantly more often in the treatment group with pertuzumab + trastuzumab + chemotherapy than in the treatment group with trastuzumab + chemotherapy. In absolute terms, the extent of the difference is minor.

In the overall consideration of the endpoints on adverse events, a disadvantage is found when pertuzumab is given in addition to trastuzumab + chemotherapy. This disadvantage is reflected in the increase in serious adverse events (SAE) as well as severe adverse events with CTCAE grade ≥ 3. In detail, this disadvantage can be seen, among other things, in the serious cardiac side effects. According to the state of medical knowledge, these are generally of high importance in treatment with anthracyclines as well as the anti-HER2 antibodies pertuzumab and trastuzumab. There is a statistically significant increase in serious cardiac insufficiencies with the addition of pertuzumab to trastuzumab + chemotherapy. However, in absolute terms, this disadvantage affects only a small proportion of patients.

For the endpoint category side effects, a lower benefit is observed for treatment with pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy.

Cross-endpoint results:

Sub-group results by age of patients (< 65 years, ≥ 65 years)

In individual endpoints on symptomatology (nausea and vomiting (end of anti-HER2 therapy) and 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) and role functioning (36-month follow-up)), a statistically significant effect modification is shown in the sub-group analysis for the characteristic age (< 65 years, ≥ 65 years). The sub-group results indicate poor effects in these endpoints for patients ≥ 65 years.

This effect modification is not shown in other patient-relevant endpoints.

A separate statement on the additional benefit based on the sub-group 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 (patients < 65 years or patients ≥ 65 years) appears problematic taking into account the reality of care. Physicians take into account not only the age of patients but also their general condition and presenting

comorbidities when deciding on therapy. This view was also expressed in the written statements of medical experts in the present procedure.

Overall assessment

For the assessment of the additional benefit of pertuzumab in combination with trastuzumab and chemotherapy for the adjuvant treatment of adult patients with HER2-positive early breast cancer with a high risk of recurrence, results on mortality (overall survival), morbidity, quality of life, and side effects compared with the appropriate comparator therapy (trastuzumab in combination with chemotherapy) are available from the APHINITY study.

With regard to the endpoint category mortality, the data on the “overall survival” endpoint are preliminary, and therefore no assessment of effectiveness can as yet be drawn for overall survival. Based on the data available, there is no statistically significant difference. For overall survival, an additional benefit of pertuzumab in combination with trastuzumab and chemotherapy is therefore not proven.

With regard to the recurrences of the disease that occurred in the study (operationalised in the endpoints DFS and recurrence rate), there was a statistically significant but only moderate positive effect of pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab in combination with chemotherapy. The prevention of recurrences is an essential therapy goal in the present curative therapy situation.

In terms of patient-reported symptomatology, neither an advantage nor a disadvantage of the treatment between the treatments can be determined overall.

In terms of patient-reported health-related quality of life, the endpoint “emotional functioning” shows a moderate advantage. This result on health-related quality of life supports the result on the overall assessment.

With respect to side effects, there is a disadvantage when pertuzumab is given in addition to trastuzumab and chemotherapy. This disadvantage is reflected in the increase in serious adverse events (SAE) as well as severe adverse events with CTCAE grade ≥ 3. In detail, there is a statistically significant increase in serious cardiac insufficiencies in the cardiac side effects; this is significant in the present therapeutic indication. However, in absolute terms, this disadvantage affects only a small proportion of patients.

In the overall consideration of the results from the APHINITY study on all patient-relevant endpoints, the positive effect with regard to the avoidance of recurrences to only a moderate extent, which is particularly relevant in the present adjuvant therapy situation, faces the significant disadvantages in the side effects, especially serious side effects. The significant disadvantages in terms of side effects are weighted against the background of the present curative therapy claim.

In a balancing decision, the G-BA has concluded that the advantage outweighs the disadvantages. Thus, in the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence, a minor additional benefit is identified for pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab in combination with chemotherapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of one study. In this study, pertuzumab in combination with trastuzumab and chemotherapy was compared with the appropriate comparator therapy in a randomised, controlled, double-blind comparison. The risk of bias at the study level is classified as low.

The endpoint-specific risk of bias is estimated to be low – except for the endpoints on patient-reported symptomatology and health-related quality of life. For the endpoints surveyed via the symptom and functional scales of the EORTC QLQ-C30 and -BR23 questionnaires, the risk of bias is considered high. This is due to a high proportion (over 10%) of patients in the relevant sub-population who were not included in the evaluation.

The aforementioned weighing decision for determining 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 (interim) results, especially on overall survival and recurrences, are based on relatively low event numbers against the background of a long median overall survival in early breast cancer and are therefore limited in their significance. Further planned interim analyses and the final analysis of overall survival data from the ongoing APHINITY study have yet to be completed.

Thus, despite the overall low risk of bias at the study and endpoint level, the reliability of the additional benefit identified is classified in the “hint” category.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the present benefit assessment of pertuzumab has 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 this 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 results on overall survival and recurrences are based on the primary data cut-off as of 19 December 2016 of the APHINITY study. At the time of the primary data cut-off, the median observation period for overall survival and recurrences was approximately 3.8 years. Because of the relatively low number of events, the significance is limited. In the APHINITY study, follow-up of overall survival and recurrences is planned until 10 years after randomisation. Further planned interim analyses are planned approx. 2.5 years and approx. 5 years after the primary analysis.

Because further clinical data from the APHINITY study are expected to be relevant for assessing the benefits of the medicinal product, it is justified to put a time limit on the period of validity of the present resolution.

Conditions of the limitation:

For the renewed benefit assessment of pertuzumab after 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 approx. 5 years after the primary analysis.

A limitation of the resolution until 2 January 2022 is considered to be appropriate.

The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long.

In accordance with Section 3, number 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment for the medicinal

product pertuzumab shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline proving an additional benefit of pertuzumab in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 5 VerfO). The possibility that a benefit assessment for the medicinal product pertuzumab can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2, Nos. 2 – 4 VerfO) remains unaffected by this.

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 will be based on the information from the dossier of the pharmaceutical company.

The number estimated by the pharmaceutical company is potentially underestimated because only the number of new breast cancer cases are used for the baseline population for 2018. It cannot be ruled out that patients who were diagnosed before the current year meet the criteria for the therapeutic indication of pertuzumab in adjuvant therapy in the current year.

In addition, patients who could be treated neoadjuvantly were excluded from the outset when the initial population was determined. 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 the underestimation is not outweighed by partially existing uncertainties.

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 Perjeta® (active ingredient: pertuzumab) at the following publicly accessible link (last access: 13 September 2018):

http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/002547/WC500140980.pdf

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

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

In older patients, disadvantageous therapy effects are seen in individual aspects of symptomatology and health-related quality of life (see study results presented above); these should be weighed up before the therapy decision is made.

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 December 2018).

Pertuzumab in combination with trastuzumab/trastuzumab
According to the product information, pertuzumab should be administered in combination with trastuzumab 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 plan for early breast cancer regardless of the timing of surgery. Pertuzumab and trastuzumab are to be started on day 1 of the first taxane-containing cycle and should be continued even if chemotherapy is stopped.

The calculation of the annual treatment costs is thus based on 18 cycles. The 18th cycle still starts in the period of one year, and the application of pertuzumab and 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 product information for trastuzumab and corresponds to the application in the comparator arm of the APHINITY study.

Trastuzumab
The information on trastuzumab is based on intravenous (i.v.) administration.

Chemotherapy regime
The information on the chemotherapy regimens is based on the doses in the APHINITY pivotal study.

Carboplatin
In the anthracycline-free therapy scheme, the dose is determined individually taking into account the kidney 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.

Treatment duration:

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	Initial dose	1.0	1.0	1.0
	In cycles (cycle = 3 weeks)	17	1.0	17
+ trastuzumab	Initial dose	1.0	1.0	1.0
	In cycles (cycle = 3 weeks)	17	1.0	17
In combination with one of the following chemotherapy regimes:				
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC), docetaxel *or* paclitaxel (q1w)				
5-fluorouracil	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Epirubicin	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Cyclophosphamide	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Docetaxel	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
or				
Paclitaxel (q1w)	In cycles (cycle = 1 week)	12.0	1.0	12.0

(Continuation)

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), docetaxel *or* paclitaxel (q1w)				
5-fluorouracil	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Doxorubicin	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Cyclophosphamide	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Docetaxel	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
or				
Paclitaxel (q1w)	In cycles (cycle = 1 week)	12.0	1.0	12.0
+ doxorubicin + cyclophosphamide (AC), docetaxel *or* paclitaxel (q1w) *or* paclitaxel (q3w)				
Doxorubicin	In cycles (cycle = 3 weeks)	4	1.0	4
Cyclophosphamide	In cycles (cycle = 3 weeks)	4	1.0	4
Docetaxel	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
or				
Paclitaxel (q1w)	In cycles (cycle = 1 week)	12.0	1.0	12.0
or				
Paclitaxel (q3w)	In cycles (cycle = 3 weeks)	4	1.0	4
+ epirubicin + cyclophosphamide (EC), docetaxel *or* paclitaxel (q1w)				
Epirubicin	In cycles (cycle = 3 weeks)	4	1.0	4
Cyclophosphamide	In cycles (cycle = 3 weeks)	4	1.0	4
Docetaxel	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
or				
Paclitaxel (q1w)	In cycles (cycle = 1 week)	12.0	1.0	12.0

+ docetaxel + carboplatin				
Docetaxel	In cycles (cycle = 3 weeks)	6	1	6
Carboplatin	In cycles (cycle = 3 weeks)	6	1	6

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Appropriate comparator therapy				
Trastuzumab	Initial dose	1.0	1.0	1.0
	In cycles (cycle = 3 weeks)	17	1.0	17
In combination with one of the following chemotherapy regimes:				
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC), docetaxel *or* paclitaxel (q1w)				
5-fluorouracil	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Epirubicin	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Cyclophosphamide	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Docetaxel	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
or				
Paclitaxel (q1w)	In cycles (cycle = 1 week)	12.0	1.0	12.0
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), docetaxel *or* paclitaxel (q1w)				
5-fluorouracil	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Doxorubicin	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Cyclophosphamide	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
Docetaxel	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
or				
Paclitaxel (q1w)	In cycles (cycle = 1 week)	12.0	1.0	12.0

(Continuation)

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
+ doxorubicin + cyclophosphamide (AC), docetaxel *or* paclitaxel (q1w) *or* paclitaxel (q3w)				
Doxorubicin	In cycles (cycle = 3 weeks)	4	1.0	4
Cyclophosphamide	In cycles (cycle = 3 weeks)	4	1.0	4
Docetaxel	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
or				
Paclitaxel (q1w)	In cycles (cycle = 1 week)	12.0	1.0	12.0
or				
Paclitaxel (q3w)	In cycles (cycle = 3 weeks)	4	1.0	4
+ epirubicin + cyclophosphamide (EC), docetaxel *or* paclitaxel (q1w)				
Epirubicin	In cycles (cycle = 3 weeks)	4	1.0	4
Cyclophosphamide	In cycles (cycle = 3 weeks)	4	1.0	4
Docetaxel	In cycles (cycle = 3 weeks)	3 to 4	1.0	3 to 4
or				
Paclitaxel (q1w)	In cycles (cycle = 1 week)	12.0	1.0	12.0
+ docetaxel + carboplatin				
Docetaxel	In cycles (cycle = 3 weeks)	6	1	6
Carboplatin	In cycles (cycle = 3 weeks)	6	1	6

Usage and consumption:

Dosage recommendations refer to use in women, as breast cancer is relatively rare in men. The body surface calculated using the Du Bois formula using an average body weight of 68.7 kg and an average body height of 1.66 m for women (according to the 2017 microcensus) = 1.76 m²[3].

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Pertuzumab	*Initial dose:*				
	840 mg	840 mg	2 × 420 mg	1	2 × 420 mg
	Maintenance dose:				
	420 mg	420 mg	1 × 420 mg	17	17 × 420 mg
+ trastuzumab	*Initial dose:*				
	8 mg/kg	549.6 mg	1 × 600 mg	1	1 × 600 mg
	Maintenance dose:				
	6 mg/kg	412.2 mg	1 × 420 mg	17	17 × 420 mg
In combination with one of the following chemotherapy regimes:					
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC) + docetaxel *or* paclitaxel (q1w)					
5-fluorouracil	500–600 mg/m²	880–1056 mg	1 × 1000 mg to 2 × 1000 mg	3 to 4	3 × 1000 mg to 8 × 1000 mg
Epirubicin	90–120 mg/m²	158.4–211.2 mg	1 × 150 mg 1 × 10 mg to 1 × 200 mg 1 × 20 mg	3 to 4	3 × 150 mg 3 × 10 mg to 4 × 200 mg 4 × 20 mg
Cyclophosphamide	500–600 mg/m²	880–1056 mg	18 × 50 mg to 22 × 50 mg	3 to 4	54 × 50 mg to 88 × 50 mg
Docetaxel	75–100 mg/m²	132–176 mg	1 × 140 mg to 1 × 160 mg 1 × 20 mg	3 to 4	3 × 140 mg to 4 × 160 mg 4 × 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 × 150 mg	12	12 × 150 mg

(Continuation)

[3] Source: German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), docetaxel *or* paclitaxel (q1w)					
5-fluorouracil	500–600 mg/m²	880–1056 mg	1 × 1000 mg to 2 × 1000 mg	3 to 4	3 × 1000 mg to 8 × 1000 mg
Doxorubicin	50 mg/m²	88 mg	1 × 100 mg	3 to 4	3 × 100 mg to 4 × 100 mg
Cyclophosphamide	500–600 mg/m²	880–1056 mg	18 × 50 mg to 22 × 50 mg	3 to 4	54 × 50 mg to 88 × 50 mg
Docetaxel	75–100 mg/m²	132–176 mg	1 × 140 mg to 1 × 160 mg 1 × 20 mg	3 to 4	3 × 140 mg to 4 × 160 mg 4 × 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 × 150 mg	12	12 × 150 mg
+ doxorubicin + cyclophosphamide (AC), docetaxel *or* paclitaxel (q1w) *or* paclitaxel (q3w)					
Doxorubicin	60 mg/m²	105.6 mg	1 × 100 mg 1 × 10 mg	4	4 × 100 mg 4 × 10 mg
Cyclophosphamide	500–600 mg/m²	880–1056 mg	18 × 50 mg to 22 × 50 mg	4	72 × 50 mg to 88 × 50 mg
Docetaxel	75–100 mg/m²	132–176 mg	1 × 140 mg to 1 × 160 mg 1 × 20 mg	3 to 4	3 × 140 mg to 4 × 160 mg 4 × 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 × 150 mg	12	12 × 150 mg
or					
Paclitaxel (q3w)	175–225 mg/m²	308 – 396 mg	1 × 300 mg 1 × 30 mg to 1 × 300 mg 1 × 100 mg	4	4 × 300 mg 4 × 30 mg to 4 × 300 mg 4 × 100 mg

(Continuation)

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
+ epirubicin + cyclophosphamide (EC), docetaxel *or* paclitaxel (q1w)					
Epirubicin	90–120 mg/m²	158.4–211.2 mg	1 × 150 mg 1 × 10 mg to 1 × 200 mg 1 × 20 mg	4	4 × 150 mg 4 × 10 mg to 4 × 200 mg 4 × 20 mg
Cyclophosphamide	500–600 mg/m²	880–1056 mg	18 × 50 mg to 22 × 50 mg	4	72 × 50 mg to 88 × 50 mg
Docetaxel	75–100 mg/m²	132–176 mg	1 × 140 mg to 1 × 160 mg 1 × 20 mg	3 to 4	3 × 140 mg to 4 × 160 mg 4 × 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 × 150 mg	12	12 × 150 mg
+ docetaxel + carboplatin					
Docetaxel	75 mg/m²	132 mg	1 × 140 mg	6	6 × 140 mg
Carboplatin	individual[4]	649 mg[5]	1 × 600 mg 1 × 50 mg	6	6 × 600 mg 6 × 50 mg

(Continuation)

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

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Trastuzumab	*Initial dose:*				
	8 mg/kg	549.6 mg	1 × 600 mg	1	1 × 600 mg
	Maintenance dose:				
	6 mg/kg	412.2 mg	1 × 420 mg	17	17 × 420 mg
In combination with one of the following chemotherapy regimes:					
+ 5-fluorouracil + epirubicin + cyclophosphamide (FEC) + docetaxel *or* paclitaxel (q1w)					
5-fluorouracil	500–600 mg/m²	880–1056 mg	1 × 1000 mg to 2 × 1000 mg	3 to 4	3 × 1000 mg to 8 × 1000 mg
Epirubicin	90–120 mg/m²	158.4–211.2 mg	1 × 150 mg 1 × 10 mg to 1 × 200 mg 1 × 20 mg	3 to 4	3 × 150 mg 3 × 10 mg to 4 × 200 mg 4 × 20 mg
Cyclophosphamide	500–600 mg/m²	880–1056 mg	18 × 50 mg to 22 × 50 mg	3 to 4	54 × 50 mg to 88 × 50 mg
Docetaxel	75–100 mg/m²	132–176 mg	1 × 140 mg to 1 × 160 mg 1 × 20 mg	3 to 4	3 × 140 mg to 4 × 160 mg 4 × 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 × 150 mg	12	12 × 150 mg
+ 5-fluorouracil + doxorubicin + cyclophosphamide (FAC), docetaxel *or* paclitaxel (q1w)					
5-fluorouracil	500–600 mg/m²	880–1056 mg	1 × 1000 mg to 2 × 1000 mg	3 to 4	3 × 1000 mg to 8 × 1000 mg
Doxorubicin	50 mg/m²	88 mg	1 × 100 mg	3 to 4	3 × 100 mg to 4 × 100 mg
Cyclophosphamide	500–600 mg/m²	880–1056 mg	18 × 50 mg to 22 × 50 mg	3 to 4	54 × 50 mg to 88 × 50 mg
Docetaxel	75–100 mg/m²	132–176 mg	1 × 140 mg to 1 × 160 mg 1 × 20 mg	3 to 4	3 × 140 mg to 4 × 160 mg 4 × 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 × 150 mg	12	12 × 150 mg

(Continuation)

Designation of the therapy	Dosage	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
+ doxorubicin + cyclophosphamide (AC), docetaxel *or* paclitaxel (q1w) *or* paclitaxel (q3w)					
Doxorubicin	60 mg/m²	105.6 mg	1 × 100 mg 1 × 10 mg	4	4 × 100 mg 4 × 10 mg
Cyclophosphamide	500– 600 mg/m²	880– 1056 mg	18 × 50 mg to 22 × 50 mg	4	72 × 50 mg to 88 × 50 mg
Docetaxel	75–100 mg/m²	132–176 mg	1 × 140 mg to 1 × 160 mg 1 × 20 mg	3 to 4	3 × 140 mg to 4 × 160 mg 4 × 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 × 150 mg	12	12 × 150 mg
or					
Paclitaxel (q3w)	175–225 mg/m²	308 – 396 mg	1 × 300 mg 1 × 30 mg to 1 × 300 mg 1 × 100 mg	4	4 × 300 mg 4 × 30 mg to 4 × 300 mg 4 × 100 mg
+ epirubicin + cyclophosphamide (EC), docetaxel *or* paclitaxel (q1w)					
Epirubicin	90–120 mg/m²	158.4– 211.2 mg	1 × 150 mg 1 × 10 mg to 1 × 200 mg 1 × 20 mg	4	4 × 150 mg 4 × 10 mg to 4 × 200 mg 4 × 20 mg
Cyclophosphamide	500– 600 mg/m²	880– 1056 mg	18 × 50 mg to 22 × 50 mg	4	72 × 50 mg to 88 × 50 mg
Docetaxel	75–100 mg/m²	132–176 mg	1 × 140 mg to 1 × 160 mg 1 × 20 mg	3 to 4	3 × 140 mg to 4 × 160 mg 4 × 20 mg
or					
Paclitaxel (q1w)	80 mg/m²	140.8 mg	1 × 150 mg	12	12 × 150 mg
+ docetaxel + carboplatin					
Docetaxel	75 mg/m²	132 mg	1 × 140 mg	6	6 × 140 mg
Carboplatin	individual[6]	660 mg[7]	1 × 600 mg 2 × 50 mg	6	6 × 600 mg 12 × 50 mg

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

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Pertuzumab	420 mg	€ 2,948.44	€ 1.77	€ 165.11	€ 2,781.56
Trastuzumab	420 mg	€ 2,215.89	€ 1.77	€ 123.28	€ 2,090.84
Trastuzumab	600 mg	€ 2,545.21	€ 1.77	€ 142.08	€ 2,401.36
Docetaxel	20 mg	€ 172.35	€ 1.77	€ 7.66	€ 162.92
Docetaxel	140 mg	€ 1,145.68	€ 1.77	€ 53.85	€ 1,090.06
Docetaxel	160 mg	€ 1,397.30	€ 1.77	€ 175.44	€ 1,220.09
Paclitaxel	30 mg	€ 115.16	€ 1.77	€ 4.94	€ 108.45
Paclitaxel	100 mg	€ 360.21	€ 1.77	€ 16.57	€ 341.87
Paclitaxel	150 mg	€ 535.25	€ 1.77	€ 24.88	€ 508.60
Paclitaxel	300 mg	€ 1,060.39	€ 1.77	€ 49.80	€ 1,008.82
Doxorubicin	10 mg	€ 39.98[8]	€ 1.77	€ 2.29	€ 35.92
Doxorubicin	20 mg	€ 68.41	€ 1.77	€ 4.54	€ 62.10
Doxorubicin	5 × 50 mg	€ 681.82[8]	€ 1.77	€ 53.06	€ 626.99
Doxorubicin	100 mg	€ 285.46[8]	€ 1.77	€ 0	€ 283.69
Epirubicin	10 mg	€ 39.12	€ 1.77	€ 1.34	€ 36.01
Epirubicin	20 mg	€ 68.23	€ 1.77	€ 2.72	€ 63.74
Epirubicin	150 mg	€ 445.06	€ 1.77	€ 20.60	€ 422.69
Epirubicin	200 mg	€ 591.36	€ 1.77	€ 27.54	€ 562.05
Cyclophosphamide	100 × 50 mg	€ 49.46[8]	€ 1.77	€ 3.04	€ 44.65
Fluorouracil	5 × 1000 mg	€ 37.12[8]	€ 1.77	€ 2.07	€ 33.28
Carboplatin	1 × 50 mg	€ 34.33	€ 1.77	€ 1.11	€ 31.45
Carboplatin	1 × 600 mg	€ 300.51	€ 1.77	€ 13.74	€ 285.00

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 December 2018

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 assessed 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.

[8] Fixed reimbursement rate

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.

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*) (status: Pending arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the *Hilfstaxe* according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the *Hilfstaxe*. The cost representation is based on the pharmacy sales price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers and carrier solutions according to the regulations in Annex 3 of the *Hilfstaxe*.

3. Bureaucratic costs

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

By letter dated 17 March 2016, received on 18 March 2016, the pharmaceutical company requested consultation in accordance with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) on, among other things, the question of appropriate comparator therapy. At its session on 10 May 2016, the Subcommittee on Medicinal Products determined the appropriate comparator therapy. The consultation meeting took place on 19 May 2016.

On 20 June 2018, the pharmaceutical company submitted a dossier for the benefit assessment of pertuzumab to the G-BA in due time in accordance with Chapter 5, Section 8, number 2, sentence 2 VerfO.

By letter dated 21 June 2018 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.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 September 2018, and the written statement procedure was initiated with publication on the website of the G-BA on 1 October 2018. The deadline for submitting written statements was 22 October 2018.

The oral hearing was held on 5 November 2018.

By letter dated 5 November 2018, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by the IQWiG was submitted to the G-BA on 29 November 2018.

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 were discussed at the session of the subcommittee on 11 December 2018, and the proposed resolution was approved.

At its session on 20 December 2018, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	10 June 2016	Determination of the appropriate comparator therapy
Working group Section 35a	31 October 2018	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	5 November 2018	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 November 2018 4 December 2018	Consultation on the dossier assessment by the IQWiG and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 December 2018	Concluding discussion of the draft resolution
Plenum	20 December 2018	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 December 2018

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

Prof. Hecken