Justification

Gemeinsamer Bundesausschuss

to 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 Dacomitinib

of 17 October 2019

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 shall pass a resolution 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 market of the active ingredient dacomitinib 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 May 2019. The pharmaceutical company 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 26 April 2019.

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 August 2019, 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 dacomitinib 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 dacomitinib.

In the light of the above and taking into account the comments 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 dacomitinib (Vizimpro®) in accordance with product information

Vizimpro, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for dacomitinib as monotherapy was determined as follows:

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R[2] or del 19[3]:

Afatinib or gefitinib or erlotinib or osimertinib

b) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19:

A patient-individual therapy depending on the activating EGFR mutation with selection of:

- Afatinib, gefitinib, erlotinib, osimertinib
- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)
- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed; *cf* Annex VI to Section K of the Pharmaceuticals Directive)
- Carboplatin in combination with nab-paclitaxel

and

- Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment).

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

[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.
[2] Exon 21 substitution mutation
[3] Exon 19 deletion

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.
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 addition to dacomitinib, cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesin, vinorelbine, afatinib, erlotinib, gefitinib, osimertinib, bevacizumab, and necitumumab are authorised for the first-line treatment of EGFR-positive non-small cell lung cancer (NSCLC), whereby carboplatinum is additionally prescribable in off-label use in the present therapeutic indication.

On 2. Non-medicinal treatment is not considered. The implementation of surgery or radiotherapy as a palliative therapy option remains unaffected.

On 3. The following resolutions and guidelines of the G-BA have been issued for medicinal therapies in the present therapeutic indication:

Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

Afatinib: Resolution of 5 November 2015

Osimertinib: Resolution of 15 September 2016

Necitumumab: Resolution of 15 September 2016

Osimertinib: Resolution of 17 January 2019

Guidelines:

Carboplatin: Resolution of 18 October 2018 on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex VI – Off-label use Part A Item III: Carboplatin for advanced non-small cell lung carcinoma (NSCLC) – combination therapy

On 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines as well as systematic reviews of clinical studies. For the present therapeutic indication, it is assumed that patients with NSCLC are in disease stages IIIB to IV (stage classification according to IASLC[4], UICC[5]) without indication for curative resection, radiation treatment, or radiochemotherapy.

[4] IASLC = International Association for the Study of Lung Cancer
[5] UICC = Union for International Cancer Control, 8th edition

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19:

The frequent activating EGFR mutations, exon 21 substitution mutation (L858R) and exon 19 deletion, comprise the majority of the present therapeutic indication with approx. 86% to 89%[6,7].

For patients with these activating EGFR mutations, current guidelines consistently recommend therapy with the tyrosine kinase inhibitors (TKI) erlotinib, gefitinib, afatinib, or osimertinib with no active ingredient being preferred. The use of tyrosine kinase inhibitors in patients with EGFR-positive NSCLC is based on the generally recognised state of medical knowledge, in particular because of the advantages in health-related quality of life, symptomatology, and certain side effects and has established itself in clinical treatment practice.

For afatinib, a significant survival benefit over cisplatin in combination with pemetrexed was found in the benefit assessment with resolution of 5 November 2015 in patients with the EGFR mutation exon 19 deletion. In contrast, for patients with the EGFR mutation exon 21 substitution (L858R) and other rare mutations, no additional benefit was derived by the G-BA.

Osimertinib represents a relatively new treatment option in this indication. In the context of the benefit assessment, the G-BA found a hint for a considerable additional benefit for this active ingredient compared with gefitinib or erlotinib in patients with the EGFR mutations exon 21 substitution and exon 19 deletion in EGFR in first-line treatment (resolution of 17 January 2019). In their written statements on the present benefit assessment, clinical experts stressed the importance of osimertinib in current care. The optimal timing for the use of osimertinib in the therapy sequence in the treatment of EGFR-positive NSCLC is the subject of ongoing discussions. Osimertinib thus has a high significance in the detection of acquired EGFR-TKI resistance as a result of an EGFR-T790M mutation (i.e. in second-line treatment after EGFR-TKI pre-treatment). Against this background, osimertinib is not considered as the only appropriate comparator therapy.

In summary, the tyrosine kinase inhibitors afatinib or erlotinib or gefitinib or osimertinib are equally suitable therapy options in the first-line treatment of NSCLC with the activating EGFR mutations L858R or del 19.

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19:

Activating EGFR mutations other than L858R or del 19 account for a considerable proportion (11–14%) of the activating EGFR mutations covered by the present therapeutic indication [6,7].

The group of activating EGFR mutations other than L858R or del 19 is highly heterogeneous. However, there is limited evidence of the individual mutations included in this group. In general, the guidelines distinguish between mutations that are tyrosine kinase inhibitor (TKI)-sensitive and those that do not respond to TKI therapy. For TKI-sensitive mutations, current guidelines recommend TKI therapy with erlotinib, gefitinib, afatinib, or osimertinib in the sense of a molecularly stratified therapy in the present disease stage.

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6 Gahr S, Stoehr R, Geissinger E, Ficker JH, Brueckl WM, Gschwendtner A et al. EGFR mutational status in a large series of Caucasian European NSCLC patients: data from daily practice. Br J Cancer 2013; 109(7): 1821–1828

7 Faehling, M., Schwenk, B., Kramberg, S., Eckert, R., Volckmar, A. L. et al. Oncogenic driver mutations, treatment, and EGFR-TKI resistance in a Caucasian population with non-small cell lung cancer: survival in clinical practice. Oncotarget 2017; 8(44): 77897–77914.

Osimertinib is also an approved treatment option for patients with activating EGFR mutations other than L858R or del 19. In the benefit assessment of osimertinib, the G-BA found no additional benefit for these patients (resolution of 17 January 2019: Patients with EGFR mutations other than L858R or del 19 (except for *de novo* T790M); resolution of 15 September 2016: patients with a *de novo* positive T790M mutation) because no suitable data on these patient groups were available in each case. Given the overall limited evidence of TKI in this patient group and considering that osimertinib is explicitly authorised for the treatment of the T790M mutation, osimertinib is determined as an appropriate comparator therapy despite the outcome of the benefit assessment.

In contrast, the activating exon 20 insertion mutation is not TKI-sensitive. For patients with the activating exon 20 insertion mutation, current guidelines recommend treatment analogous to EGFR wild-type patients. Accordingly, these patients are treated with a platinum-based combination chemotherapy with a third-generation cytostatic agent. In accordance with the Pharmaceuticals Directive (last revised: 18 October 2018): Annex VI – Off-label use Part A Item III: “Carboplatin for advanced non-small cell lung carcinoma (NSCLC) – combination therapy, carboplatin is prescribable, whereby the selection of the platinum component (carboplatin or cisplatin) should, in individual cases, be based on the different toxicity profile of the two substances as well as on the existing comorbidities.

Furthermore, nab-paclitaxel in combination with carboplatin is considered to be another appropriate therapy option for these patients.

For patients with reduced general condition, however, the toxicity profile of platinum-based combination chemotherapy must be weighed against the expected benefit, taking into account patient-individual criteria. As an alternative, patients with ECOG performance status 2 may be considered for monochemotherapy with gemcitabine or vinorelbine, which is considered appropriate for this group of patients in addition to platinum-based combination chemotherapy.

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

Change of the appropriate comparator therapy:

In contrast to the original determination of the appropriate comparator therapy, this is supplemented by osimertinib in the present resolution for patient group a).

Similarly, compared with the original determination of the appropriate comparator therapy for patient group b), this resolution changes the appropriate comparator therapy by adding osimertinib to the patient-individual therapy depending on the activating EGFR mutation.

This takes particular account of the written statements of clinical experts submitted in the present benefit assessment procedure.

The present assessment of the additional benefit of dacomitinib remains unaffected by this.

2.1.3 Extent and probability of the additional benefit

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

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19:

For the treatment of adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19, an additional benefit is not proven.

Justification:

To demonstrate the additional benefit of dacomitinib in the first-line therapy of locally advanced or metastatic NSCLC with EGFR activating mutations, the pharmaceutical company presented the results of the ARCHER 1050 study.

ARCHER 1050 is a multi-centre, open, randomised controlled study in which dacomitinib is compared with gefitinib. The ongoing global study, which started in May 2013, includes adult patients without pre-treatment for advanced or metastatic stage non-small cell lung carcinoma (NSCLC) with a World Health Organisation Performance Status (WHO-PS) of 0 or 1. Since the end of (neo-) adjuvant therapy, patients must have had a disease-free interval of at least 12 months or a *de novo* diagnosis of the advanced stage. In accordance with the inclusion criteria of the ARCHER 1050 study, only patients with tumours with the EGFR mutation exon 21 substitution mutation (L858R) or exon 19 deletion (del 19) were included. The inclusion of patients with the additional mutation T790M in exon 20 was permitted. Patients with tumours with activating EGFR mutations other than L858R and del 19 were excluded from the study.

The 452 patients included were randomised 1:1 into the dacomitinib arm (N = 227) and the gefitinib arm (N = 225) and stratified by activating EGFR mutation (exon 19 deletion vs exon 21 substitution) and ethnicity (Japanese vs mainland Chinese vs other East Asian vs non-Asian).

Treatment with the trial medication should last for 48 months or until disease progression, the start of a new cancer therapy, or discontinuation for other reasons (e.g. because of AE or at the discretion of the patient). Patients without disease progression were able to continue treatment beyond 48 months at the discretion of the study physician. In individual cases, even with disease progression, treatment with the study medication was continued as long as patients had a clinical benefit according to the assessment of the study physician. A change from one study medication to another in the case of disease progression was not permitted.

ARCHER 1050 is being conducted in 90 study centres in Asia and Europe. Predominantly Asian patients are examined; they represent approx. 3/4 of the study population.

Three data cut-offs are currently available: the planned analysis for the primary endpoint progression-free survival (PFS) of 29 July 2016 and the planned final evaluation of overall survival of 17 February 2017. Results for all patient-relevant endpoints are available for the latter data section. In addition, an additional data cut-off on overall survival (from 13 May 2019) was submitted by the pharmaceutical company as part of the written statement procedure. Because this analysis is not a pre-specified data cut-off in the study protocol and the data cut-off of 17 February 2017 also contains the final analysis of the endpoint overall survival, the data cut-off of 17 February 2017 is used for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

In the ARCHER 1050 study, overall survival was defined as the time between randomisation and death regardless of the underlying cause of death.

For overall survival, there is a statistically significant difference in favour of dacomitinib between the two treatment arms (hazard ratio (HR)): 0.76 [95% confidence interval (CI):

0.58; 0.99]; p value 0.044). The median overall survival in the intervention arm was 7.3 months longer than in the control arm (34.1 vs 26.8 months).

When interpreting the present results in relation to the difference in the median overall survival, it should be noted that in the corresponding Kaplan-Meier curves of overall survival in both study arms, there is a noticeably high number of censorships in the area of the median. There are therefore relevant uncertainties in the interpretation of the overall survival results. The results show a statistically significant effect, the extent of which cannot be conclusively assessed because of the uncertainties. It should also be noted that the Kaplan-Meier curves intersect at Month 12.

Morbidity

Progression-free survival (PFS)

In the ARCHER 1050 study, progression-free survival was the primary endpoint and was defined as the time between randomisation and disease progression (determined by a blinded independent radiological committee (IRC) using RECIST criteria version 1.1) or death regardless of the underlying cause.

In the intervention arm, there was a statistically significant increase in median PFS of 5.5 months compared with the control arm (median of 14.7 vs 9.2 months; HR: 0.59; [95% CI: 0.47; 0.74]; p value < 0.0001).

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was collected as an independent endpoint via the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint.

For the interpretation of the PFS results, the data available on morbidity and health-related quality of life are used. Data on morbidity and health-related quality of life are potentially relevant in this respect, especially when, as in the present case, a radiologically determined disease progression is associated with effects on morbidity and/or quality of life.
The data available from the ARCHER 1050 study show an overall adverse effect of dacomitinib compared with gefitinib in terms of symptomatology and health-related quality of life. Accordingly, prolonged PFS under dacomitinib was not associated with an advantage in terms of morbidity or quality of life.

In summary, the data available do not suggest that the statistically significant prolongation of progression-free survival under dacomitinib – radiologically determined disease progression according to the RECIST criteria – is associated with an improvement in morbidity or health-related quality of life.

The results on the progression-free survival endpoint are not used in this assessment.

Symptomatology

In the ARCHER 1050 study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the lung cancer-specific additional module QLQ-LC13.

The survey was conducted regularly during treatment (weekly in the first treatment cycle and then once a month), at the end of treatment, and 28 to 35 days after the end of treatment.

For the benefit assessment, in the dossier, the pharmaceutical company presented responder analyses for the time until first deterioration and the time until once confirmed deterioration.
For the present assessment, the evaluation of the time until once confirmed deterioration of the symptomatology is used (defined *post hoc* as the increase of the score by at least 10 points compared with baseline measured on at least two consecutive rounds). This evaluation was pre-specified for some of the scales considered in the study. For the remaining scales, it was performed *post hoc*.

For the endpoints pain, loss of appetite, diarrhoea, sore mouth, dysphagia, peripheral neuropathy, alopecia and other pain there was a statistically significant difference to the disadvantage of dacomitinib compared with gefitinib. For all further endpoints presented, there was no statistically significant difference between the study arms.

Overall, treatment with dacomitinib shows a clear disadvantage in terms of symptomatology compared with treatment with gefitinib.

Health status (EQ-5D visual analogue scale)

The general health status was assessed using the visual analogue scale of the EQ-5D. The survey was conducted regularly during treatment (weekly in the first treatment cycle and then once a month), at the end of treatment, and 28 to 35 days after the end of treatment.

For the benefit assessment, the pharmaceutical company presented responder analyses for the time to first deterioration and the time to once confirmed deterioration by ≥ 10 points of the VAS score compared with baseline. These responder analyses were not pre-specified in the ARCHER 1050 study.

These responder analyses were not used in the IQWiG dossier evaluation because the study underlying the derivation of the minimal important difference (MID) (Pickard *et al.*, 2007) of the IQWiG was classified as unsuitable to validate the MID. This is justified on one hand by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID. The anchors ECOG-PS and FACT-G total score of the IQWiG used in the study are also not considered suitable for deriving the MID.

Instead of the responder analyses, the dossier evaluation of the IQWiG used the analyses of mean value differences. Within the framework of these analyses, no statistically significant difference between the treatment arms is found for the time until permanent deterioration.

In view of the fact that responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with an analysis of standardised mean value differences and taking into account that the validation study in question has already been used in earlier evaluations, the G-BA nevertheless uses the responder analyses in the present assessment to assess the effects on symptomatology. The evaluations of the time until the first confirmed deterioration are used.

These responder analyses show a statistically significant difference to the disadvantage of dacomitinib between the treatment arms.

Quality of life

In the ARCHER 1050 study, the functional scales of the disease-specific questionnaire EORTC QLQ-C30 were used to assess the health-related quality of life.

The survey was conducted regularly during treatment (weekly in the first treatment cycle and then once a month), at the end of treatment, and 28 to 35 days after the end of treatment.

For the benefit assessment, in the dossier, the pharmaceutical company presented responder analyses for the time until first deterioration and the time until once confirmed deterioration.
For the present assessment, the evaluation of the time until once confirmed deterioration of health-related quality of life is used (defined *post hoc* as the decrease of the score by at least 10 points compared with baseline measured on at least two consecutive rounds).

The endpoints of global health status, role function, cognitive function, and social function showed a statistically significant difference to the disadvantage of dacomitinib compared with gefitinib.

There was no statistically significant difference between the study arms for the endpoints physical function and emotional function.

Overall, treatment with dacomitinib shows a clear disadvantage in terms of health-related quality of life compared with treatment with gefitinib.

Side effects

Adverse events (AE)

The AE were surveyed until the start of a new cancer therapy but not more than 28 to 35 days after the end of treatment.

In the ARCHER 1050 study, 99.6% of the patients in the intervention arm and 98.2% in the comparator arm experienced an adverse event.

Serious adverse events (SAE)

SAE were surveyed up to 28 days after the end of treatment.

For the serious adverse events, there was no statistically significant difference between the study arms.

Severe adverse events (CTCAE grade 3 or 4)

A statistically significant disadvantage of dacomitinib was found with regard to severe adverse events with CTCAE grade 3 or 4.

Discontinuation because of AE

For the endpoint “therapy discontinuation because of an AE”, there was no statistically significant difference between the study arms.

Specific AE

Specific AE were selected according to the methodology of the IQWiG using events based on frequency and differences between treatment arms and taking into account patient relevance.
Dacomitinib showed a statistically significant advantage compared with gefitinib in terms of the specific AE back pain and chest pain as well as the specific AE (CTCAE grade 3 or 4) investigations.
In contrast, dacomitinib showed a statistically significant disadvantage compared with gefitinib with respect to the specific AE stomatitis, dry skin, alopecia, conjunctivitis, respiratory, thoracic and mediastinal disorders, eye diseases, and metabolism and nutrition disorders as well as the specific AE (CTCAE grade 3 or 4) diarrhoea, skin and subcutaneous

tissue disorders, and paronychia. In the overall view of the endpoints for specific AE, adverse effects clearly predominate in treatment with dacomitinib.

In the side effects category, a relevant disadvantage of dacomitinib compared with gefitinib can be observed in the overall view.

Overall assessment

For the assessment of the additional benefit of dacomitinib, results from the open-label, randomised, controlled ARCHER 1050 study in comparison to gefitinib on mortality (overall survival), morbidity (symptomatology and health status), quality of life, and side effects are available.

In the endpoint category mortality, the results available for the endpoint overall survival show a statistically significant effect in favour of dacomitinib compared with gefitinib. However, because of a high number of censorships of the Kaplan-Meier curves in the area of the median, there are relevant uncertainties in the interpretation of the overall survival results. The extent of this effect can thus not be conclusively assessed. It should also be noted that the Kaplan-Meier curves intersect.

The advantage in the overall survival endpoint is faced by a number of unfavorable effects in the categories of morbidity, health-related quality of life, and adverse events.

Thus, the results for the category morbidity with regard to symptomatology show exclusively negative effects of treatment with dacomitinib compared with gefitinib. These symptoms reported by patients include pain, loss of appetite, diarrhoea, sore mouth, dysphagia, peripheral neuropathy, alopecia, and other pain. Overall, there is a clear disadvantage with regard to symptomatology. Also for the endpoint of general health status (measured by EQ-5D VAS), there is an unfavorable effect of dacomitinib compared with gefitinib.

Also, for health-related quality of life, only unfavorable effects of dacomitinib treatment were observed for the patient-reported endpoints of global health status, role function, cognitive function, and social function. In the category of health-related quality of life, dacomitinib also has a clear disadvantage compared with gefitinib.

In terms of side effects, with respect to the endpoint severe adverse events (CTCAE grade 3 or 4), there is a clear disadvantage of dacomitinib compared with gefitinib. No differences are found for the endpoints serious AE and discontinuation because of AE. In the case of specific AE, on the other hand, negative effects clearly predominate. Thus, in the side effects category, relevant unfavorable effects of dacomitinib compared with gefitinib can be identified.

In the overall view, the positive effect of dacomitinib in overall survival (the extent of which cannot be conclusively assessed) is countered by a large number of (in some cases clearly) negative effects. These are found across the board in the endpoint categories of morbidity, health-related quality of life, and side effects. In a balancing decision, the G-BA concluded that the negative effects of dacomitinib outweigh the positive effect on overall survival. It is thus concluded that there is no additional benefit of dacomitinib compared with gefitinib in the first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19.

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19:

For the treatment of adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19, an additional benefit is not proven.

Justification:

For adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19, no data were provided to assess the additional benefit of dacominitib compared with the appropriate comparator therapy. In the ARCHER 1050 study presented, only patients with the activating EGFR mutations L858R or del 19 were examined.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Vizimpro® with the active ingredient dacomitinib. Dacomitinib, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations.

In the therapeutic indication to be considered, the following patient groups were distinguished:

a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19

b) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19

About patient group a)

The appropriate comparator therapy was determined by the G-BA as follows:

Afatinib or gefitinib or erlotinib or osimertinib

For this patient group, the pharmaceutical company presents results from the open, randomised, controlled ARCHER 1050 study in which dacomitinib is compared with gefitinib. The ARCHER 1050 study included adult patients without previous treatment for advanced or metastatic NSCLC with the EGFR mutations L858R or del 19.

In the endpoint category mortality, the results available for the endpoint overall survival showed a statistically significant effect in favour of dacomitinib compared with gefitinib, the extent of which cannot be conclusively assessed.

The results in the endpoint categories morbidity and health-related quality of life showed exclusively numerous unfavorable effects of treatment with dacomitinib.

In terms of side effects, with respect to the endpoint severe adverse events (CTCAE grade 3 or 4), there is a clear disadvantage of dacomitinib compared with gefitinib. No differences are found for the endpoints serious AE and discontinuation because of AE. In the case of specific AE, on the other hand, negative effects clearly predominate. Thus, in the side effects category, relevant unfavorable effects of dacomitinib compared with gefitinib can be identified.

In the overall view, the positive effect of dacomitinib in overall survival (the extent of which cannot be conclusively assessed) is countered by a large number of (in some cases clearly)

negative effects. In a balancing decision, the G-BA concluded that the negative effects of dacomitinib outweigh the positive effect on overall survival. It is thus concluded that there is no additional benefit of dacomitinib compared with gefitinib in the first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19.

About patient group b)

The appropriate comparator therapy was determined by the G-BA as follows:

A patient-individual therapy depending on the activating EGFR mutation with selection of:

- Afatinib, gefitinib, erlotinib, osimertinib
- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)
- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed; *cf* Annex VI to Section K of the Pharmaceuticals Directive)
- Carboplatin in combination with nab-paclitaxel

and

- Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment).

For patients with activating EGFR mutations other than L858R or del 19, no data were provided to assess the additional benefit of dacominitib over the appropriate comparator therapy. In the ARCHER 1050 study presented, only patients with the activating EGFR mutations L858R or del 19 were examined.
For the treatment of adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19, an additional benefit is thus not proven.

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

In order to enable a consistent consideration of the number of patients, taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication locally advanced or metastatic NSCLC with activating EGFR mutations (pembrolizumab: 19 September 2019; osimertinib: 17 January 2019; atezolizumab: 16 March 2018; nivolumab: 20 October 2016; osimertinib: 15 September 2016), the G-BA uses the following derivation of patient numbers:

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

For the number of German patients with lung cancer, the incidence for 2019 (56,979) patients from the previous resolution on pembrolizumab (resolution of 19 September 2019) is used as the basis for the calculations.

This patient group is limited to the target population via eight calculation steps:

1. The proportion of lung cancer patients with NSCLC is approx. 80.3–82%.[8]

2. Of these, 61.6–66.1% are stage IIIB/IV patients.[8]

3. First-line therapy is performed in 76.9 to 78.5% of cases.[9]

4. The proportion of activating EGFR mutations is approx. 4.9–10.3%.[8]

5. Patient group a: Adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19: Sum of the proportions of L858R (23.7–27.3%) and del 19 (61.3–61.9%) = approx. 86–89%[6,7]

6. Patient group b: Adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19 = 11–14%

7 Number of SHI patients: 85.9% [10]

For

- Patient group a: Adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19:

  790 to 1910 patients

- Patient group b: Adult patients with locally advanced or metastatic NSCLC with rare activating EGFR mutations:

  100 to 300 patients

In contrast to the resolution on Osimertinib of 17 January 2019, the proportional values for calculation steps 5 and 6 are stated differently. This is mainly because the information available on the respective proportional values was also based on a current source[7].

[8] Resolution on osimertinib of 17 January 2019
[9] Resolution on pembrolizumab of 3 August 2017
[10] Resolution on pembrolizumab of 19 September 2019

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 Vizimpro® (active ingredient: dacomitinib) at the following publicly accessible link (last access: 26 August 2019):

https://www.ema.europa.eu/documents/product-information/vizimpro-epar-product-information_de.pdf

Treatment with dacomitinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and pneumology, specialists in pulmonary medicine, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with non-small cell lung carcinoma.

If the use of dacomitinib is considered, the EGFR mutation status must be determined by a validated test procedure.

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 October 2019).

The cost estimate is based on the dosage recommended in the product information for Vizimpro® (last revised: April 2019) for treatment with dacomitinib.

According to the product information (Cisplatin Accord (last updated: April/2015)), the dosage of cisplatin varies depending on the combination partner. According to the product information of the combination partners, the single dose of cisplatin in combination with vinorelbine or gemcitabine is 75–100 mg/m^2, in combination with docetaxel or pemetrexed, 75 mg/m^2, and in combination with paclitaxel, 80 mg/m^2.

Carboplatin is based on a cycle duration of 3 weeks. For the use of carboplatin in the off-label indication “combination therapy for advanced NSCLC”, the dosage specified in Annex VI of the Pharmaceuticals Directive is up to 500 mg/m² or AUC 6.0 (Area Under the Curve). For the use of carboplatin in combination with nab-paclitaxel, the dosage of AUC 6.0 is also used according to the product information.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Dacomitinib	1 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Appropriate comparator therapy				
a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19:				
Afatinib	1 × daily	365	1	365
Erlotinib	1 × daily	365	1	365
Gefitinib	1 × daily	365	1	365
Osimertinib	1 × daily	365	1	365
b) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19:				
Afatinib, gefitinib, erlotinib, osimertinib				
Afatinib	1 × daily	365	1	365
Erlotinib	1 × daily	365	1	365
Gefitinib	1 × daily	365	1	365
Osimertinib	1 × daily	365	1	365
Cisplatin or carboplatin in combination with a third generation cytostatic agent				
Cisplatin	1 × per 21-day cycle	17 cycles	1	17
Carboplatin	1 × per 21-day cycle	17 cycles	1	17
+ vinorelbine	2 × per 21-day cycle	17 cycles	2	34
+ gemcitabine	2 × per 21-day cycle	17 cycles	2	34
+ docetaxel	1 × per 21-day cycle	17 cycles	1	17
+ paclitaxel	1 × per 21-day cycle	17 cycles	1	17
+ pemetrexed	1 × per 21-day cycle	17 cycles	1	17
Carboplatin in combination with nab-paclitaxel				
Carboplatin	1 × per 21-	17 cycles	1	17

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	day cycle			
+ nab-paclitaxel	3 × per 21-day cycle	17 cycles	3	51
Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment)				
Gemcitabine	3 × per 28-day cycle	13 cycles	3	39
Vinorelbine	1 × per 7-day cycle	52 cycles	1	52

Usage and consumption:

The body surface calculated using the Du Bois formula using an average body weight of 77.0 kg and an average body height of 1.72 m (according to the 2017 microcensus) = 1.90 m² (calculated to 2 decimal places). Differences between women and men were not to be considered because of the therapeutic indication. [11]

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
Medicinal product to be assessed					
Dacomitinib	45 mg	45 mg	1 × 45 mg	365	365 × 45 mg
Appropriate comparator therapy					
a) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or del 19:					
Afatinib or gefitinib or erlotinib or osimertinib					
Afatinib	40 mg	40 mg	1 × 40 mg or	365	365 × 40 mg
Erlotinib	150 mg	150 mg	1 × 150 mg	365	365 × 150 mg
Gefitinib	250 mg	250 mg	1 × 250 mg	365	365 × 250

11 https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
					mg
Osimertinib	80 mg	80 mg	1 × 80 mg	365	365 × 80 mg
b) Adult patients with first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or del 19:					
Afatinib, gefitinib, erlotinib, osimertinib					
Afatinib	40 mg	40 mg	1 × 40 mg or	365	365 × 40 mg
Erlotinib	150 mg	150 mg	1 × 150 mg	365	365 × 150 mg
Gefitinib	250 mg	250 mg	1 × 250 mg	365	365 × 250 mg
Osimertinib	80 mg	80 mg	1 × 80 mg	365	365 × 80 mg
Cisplatin or carboplatin in combination with a third generation cytostatic agent					
Cisplatin	75 mg/m^2 = 142.5 mg	142.5 mg	1 × 100 mg + 1 × 50 mg	17	17 × 100 mg + 17 × 50 mg
	80 mg/m^2 = 152 mg	152 mg	1 × 100 mg + 1 × 50 mg + 1 × 10 mg	17	17 × 100 mg + 17 × 50 mg + 17 × 10 mg
	100 mg/m^2 = 190 mg	190 mg	2 × 100 mg	17	34 × 100 mg
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17	17 × 600 mg + 17 × 450 mg
+ vinorelbine	25 mg/m^2 = 47.5 mg	47.5 mg	1 × 50 mg	34	34 × 50 mg
	30 mg/m^2 = 57 mg	57 mg	1 × 50 mg + 1 × 10 mg	34	34 × 50 mg + 34 × 10 mg
+	1,250	2,375 mg	1 × 2,000 mg +	34	34 × 2,000

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
gemcitabine	mg/m² = 2,375 mg		2 × 200 mg		mg + 68 × 200 mg
+ docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 × 160 mg	17	17 × 160 mg
+ paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 × 100 mg + 1 × 150 mg	17	34 × 100 mg + 17 × 150 mg
+ pemetrexed	500 mg/m² = 950 mg	950 mg	2 × 500 mg	17	34 × 500 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17	17 × 600 mg + 17 × 450 mg
+ nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 × 100 mg	51	102 × 100 mg
Monotherapy with gemcitabine or vinorelbine (only for patients with ECOG performance status 2 as an alternative to platinum-based combination treatment)					
Gemcitabine	1000 mg/m² = 1900 mg	1900 mg	1 × 2000 mg	39	39 × 2000 mg
Vinorelbine	25 mg/m² = 47.5 mg 30 mg/m² = 57 mg	47.5 mg 57 mg	1 × 50 mg 1 × 50 mg + 1 × 10 mg	52 52	52 × 50 mg - 52 × 50 mg + 52 × 10 mg

Costs:

Costs of the medicinal product:

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

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Dacomitinib 45 mg	30 FCT	€4,819.17	€ 1.77	€ 271.95	€ 4,545.45
Appropriate comparator therapy					
Afatinib 40 mg	28 FCT	€ 2,514.93	€ 1.77	€ 140.35	€ 2,372.81
Carboplatin 600 mg	1 ISC	€ 300.51	€ 1.77	€ 13.74	€ 285.00
Carboplatin 450 mg	1 ISC	€ 227.91	€ 1.77	€ 10.29	€ 215.85
Cisplatin 100 mg	1 ISC	€ 76.26	€ 1.77	€ 3.10	€ 71.39
Cisplatin 50 mg	1 ISC	€ 47.37	€ 1.77	€ 1.73	€ 43.87
Cisplatin 10 mg	1 ISC	€ 17.20	€ 1.77	€ 0.30	€ 15.13
Docetaxel 160 mg	1 ISC	€ 1,397.30	€ 1.77	€ 175.44	€ 1,220.09
Erlotinib 150 mg	30 FCT	€ 2,887.67	€ 1.77	€ 161.64	€ 2,724.26
Gefitinib 250 mg	30 FCT	€ 1,587.48	€ 1.77	€ 74.90	€ 1,510.81
Gemcitabine 2,000 mg	1 ISC	€ 193.90	€ 1.77	€ 8.68	€ 183.45
Gemcitabine 200 mg	1 ISC	€ 28.51	€ 1.77	€ 0.83	€ 25.91

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
nab-paclitaxel	1 vial	€ 429.03	€ 1.77	€ 23.15	€ 404.11
Osimertinib	30 FCT	€ 6,155.86	€ 1.77	€ 348.29	€ 5,805.80
Paclitaxel 100 mg	1 ISC	€ 360.21	€ 1.77	€ 16.57	€ 341.87
Paclitaxel 150 mg	1 ISC	€ 535.25	€ 1.77	€ 24.88	€ 508.60
Pemetrexed	1 PIS	€ 2,533.24	€ 1.77	€ 558.64	€ 1,972.83
Vinorelbine 50 mg	10 ISC	€ 1,424.23	€ 1.77	€ 67.07	€ 1,355.39
Vinorelbine 10 mg	10 ISC	€ 293.68	€ 1.77	€ 13.42	€ 278.49
Abbreviations: FCT = film-coated tablets; ISC = infusion solution concentrate; PIS = powder for the preparation of an infusion solution					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 October 2019

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.

Non-prescription medicinal products are subject to the regulations on the prescribability of non-prescription medicinal products (OTC medicinal products) at the expense of statutory health insurance. These medicinal products are not subject to the current medicinal product price regulation but rather, in accordance with Section 129, paragraph 5a of the German Social Code, Book V, (SGB V) when a non-prescription medicinal product is sold and invoiced in accordance with Section 300 SGB V, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

Cost per package	Costs after deduction of statutory Rebates[12]	Costs per service[13]	Treatment days per year	Cost per patient per year
Cisplatin				
Anti-emetic treatment				
In clinical practice, appropriate anti-emetic treatment is established before and/or after cisplatin administration. The product information of cisplatin does not contain any concrete information on this, which is why the necessary costs cannot be quantified.				
Forced diuresis with mannitol 10% infusion solution, 37.5 g/day				
10 × 500 ml: € 106.22	€ 91.10 (€ 5.31; € 9.81)	€ 9.11	17	€ 154.87
Hydration: sodium chloride 0.9% infusion solution, 3–4.4 l/day				
10 × 1,000 ml: € 35.47 10 × 500 ml: € 22.72	€ 32.58 (€ 1.77; € 1.12) € 20.89 (€ 1.14; € 0.69)	€ 9.77–15.12	17	€ 166.16–257.06
Pemetrexed				
Pre-medication: Dexamethasone 2 × 4 mg/day, oral				
100 × 4 mg: € 79.21 (FB)	€ 72.04 (€ 1.77; € 5.40)	€ 1.44	51	€ 73.48
Folic acid: 350 – 1,000 µg/day[14], oral				
100 × 400 µg: € 15.55	€ 12.63 (€ 0.78; € 2.14)	€ 0.13 – 0.25	365	€ 46.10 – 92.20
Vitamin B12: 1,000 µg/day, i.m.				
10 × 1,000 µg: € 7.40 (FB)	€6.71 (€ 0.37; € 0.32)	€ 0.67	6	€ 4.03
Paclitaxel				
Pre-medication: Dexamethasone 2 × 20 mg/day, oral				
20 × 20 mg: € 53.75 (FB)	€ 51.98 (€ 1.77; €0.00)	€ 5.20	17	€ 88.37
Antihistamine: Dimetindene 1 mg per 10 kg BW, i.v.				
5 × 4 mg: € 18.56	€ 14.82 (€1.77; € 1.97)	€ 5.93[15]	17	€ 100.78
Ranitidine: 50 mg/day, i.v.				
5 × 50 mg: € 15.02	€ 13.06 (€1.77; € 0.19)	€ 2.61	17	€ 44.40

Other services covered by SHI funds:

12 Section 130 SGB V and Section 130a SGB V

13 Proportionate costs of costs per package for consumption per treatment day

14 The cost of folic acid is calculated on the basis of the single dose of 400 µg of the non-divisible tablets available for cost calculation, based on a dose range of 400–800 µg per day, even if a dose range of 350–1000 µg is specified in the product information.

15 For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average height: 1.72 m, average body weight: 77 kg).
Source: German Federal Office For Statistics, Wiesbaden 2018:
https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

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 retail price publicly accessible in the directory services in accordance with 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"] (last revised: 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 products 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 retail price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of 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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 7 November 2017.

The appropriate comparator therapy established by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 12 February 2019.

On 26 April 2019, the pharmaceutical company submitted a dossier for the benefit assessment of dacomitinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 26 April 2019 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 dacomitinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 July 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 August 2019. The deadline for submitting written statements was 22 August 2019.

The oral hearing was held on 9 September 2019.

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 8 October 2019, and the proposed resolution was approved.

At its session on 17 October 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	7 November 2017	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	12 February 2019	Redefinition of the appropriate comparator therapy
Working group Section 35a	3 September 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	9 September 2019	Conduct of the oral hearing
Working group Section 35a	18 September 2019 2 October 2019	Advice on the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG), evaluation of the written statement procedure
Subcommittee Medicinal product	8 October 2019	Concluding discussion of the proposed resolution
Plenum	17 October 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 October 2019

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

Prof Hecken