Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII –Resolution on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V Brigatinib

of 4 July 2019

Contents

1. Legal basis 2

2. Key points of the resolution 2

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy 3

2.1.1 Approved therapeutic indication of brigatinib (Alunbrig®) in accordance with the product information 3

2.1.2 Appropriate comparator therapy 3

2.1.3 Extent and probability of the additional benefit 5

2.1.4 Summary of the assessment 7

2.2 Number of patients or demarcation of patient groups eligible for treatment 8

2.3 Requirements for a quality-assured application 8

2.4 Treatment costs 9

3. Bureaucratic costs 10

4. Process sequence 10

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. Requirement 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 brigatinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 January 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 15 January 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 15 April 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 brigatinib 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, 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 brigatinib.

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

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

2.1.1 Approved therapeutic indication of brigatinib (Alunbrig®) in accordance with the product information

Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.

2.1.2 Appropriate comparator therapy

For brigatinib for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) in adult patients previously treated with crizotinib, the appropriate comparator therapy is:

ceritinib or alectinib

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 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 terms of authorisation status, for the treatment of (ALK)-positive, non-small cell lung cancer (NSCLC), the chemotherapeutic agents carboplatin, cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, and vinorelbine, the protein kinase inhibitors afatinib, alectinib, dabrafenib, ceritinib, erlotinib, gefitnib, lorlatinib, nintedanib, osimertinib, and trametinib, and the

[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.

antibodies atezolizumab, bevacizumab, nivolumab, pembrolizumab, and pamucirumab are available.

Because ALK-positive tumours are usually EGFR-negative, therapy options based on an EGFR mutation cannot be considered.

On 2. With regard to non-medicinal treatments, radiation therapy (e.g. local one-sided stereotactic radiation) is a therapeutic option for the treatment of metastases. Radiotherapy is a patient-individual therapy option potentially available to all patients and is mainly used for palliative symptom control depending on the localisation and symptomatology of the metastases, which is why it was not included in the appropriate comparator therapy.

On 3. With regard to ALK inhibitors, the following resolutions of the G-BA are available in the therapeutic indication ALK-positive NSCLC previously treated with crizotinib:

- Resolution of 19 October 2017 on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V – alectinib
- Resolution of 16 March 2017 on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V – ceritinib

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.

In accordance with current guideline recommendations, in particular the S3 guideline, ALK-positive patients will be offered second generation NSCLC ALK inhibitors following the failure of crizotinib-/ALK-TKI. With the ALK inhibitors ceritinib and alectinib, two ALK-specific treatment options are available for ALK-positive NSCLC after prior treatment with crizotinib, which is why further therapeutic options have no relevant significance in the therapeutic indication.

In the corresponding benefit assessment of the G-BA for ceritinib, a hint for a considerable additional benefit compared with monochemotherapy with docetaxel or pemetrexed was found for patients who are eligible for treatment with docetaxel or pemetrexed (resolution of the G-BA of 16 March 2017 – reassessment at the end of the initial temporary resolution). Ceritinib showed a clear improvement in symptoms and also advantages in partial aspects of health-related quality of life and side effects compared with monochemotherapy (docetaxel or pemetrexed). in patients with advanced ALK-positive NSCLC who had received platinum-based combination chemotherapy followed by crizotinib as previous therapy. For overall survival, no additional benefit for ceritinib was demonstrated; a high number of patients switched from chemotherapy to follow-up treatment with ceritinib (cross-over).

In the benefit assessment for alectinib, a hint for a minor additional benefit compared with monochemotherapy with docetaxel or pemetrexed was found for patients who are eligible for treatment with docetaxel or pemetrexed (resolution of the G-BA of 19 October 2017). Alectinib showed improvements in side effects compared with monochemotherapy (docetaxel or pemetrexed) in patients with advanced ALK-positive NSCLC who had received platinum-based combination chemotherapy followed by crizotinib as previous therapy. For overall survival, no additional benefit was proven for alectinib; analogous to the resolution for ceritinib, a high number of patients switched from the chemotherapy treatment group to a follow-up treatment with alectinib (cross-over), whereby the result for overall survival is subject to a potentially strong bias.

Overall, the indication of ALK-positive NSCLC is characterised by a high dynamic of medicinal options. As a result of this, the significance of chemotherapy has decreased significantly.

In the treatment of ALK-positive NSCLC previously treated with crizotinib, the role of chemotherapy with docetaxel or pemetrexed has clearly decreased in favour of ALK-TKI monotherapy. Current guidelines in the molecularly stratified therapy of pretreated ALK-positive NSCLC thus recommend ceritinib as well as alectinib as a further therapy option. According to the statements made by medical societies in the present procedure, the therapeutic significance of alectinib in the daily clinical care of patients with ALK-positive NSCLC previously treated with crizotinib is also classified as a further standard therapy. Taking into account the hints for a minor additional benefit for alectinib given in the G-BA resolution of 19 October 2017 as well as current guideline recommendations and the written statements of medical associations submitted in the present procedure, the monotherapies of ceritinib and alectinib are therefore identified as equally appropriate comparator therapies for the treatment of ALK-positive advanced NSCLC in adult patients pretreated with crizotinib.

The high therapeutic dynamics are also reflected in the previous therapies of ALK-positive NSCLC. The significance of mono- or combination chemotherapy has thus shifted significantly in favour of the ALK-TKI monotherapies crizotinib and alectinib.

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

Change of the appropriate comparator therapy

This resolution supplements the originally established appropriate comparator therapy ceritinib with the ALK-TKI alectinib and takes the following form:
For brigatinib for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) in adult patients previously treated with crizotinib, the appropriate comparator therapy is “ceritinib or alectinib”

This takes into account the hint for a minor additional benefit for alectinib given in the G-BA resolution of 19 October 2017. The current guideline recommendations and the statements of medical societies regarding the therapeutic significance of therapy with alectinib made in the present procedure, which state that alectinib is another standard therapy in the clinical care of patients ALK-positive NSCLC previously treated with crizotinib, have also been taken into account.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

Justification:

There are no direct comparative studies or adjusted indirect comparisons between a common bridge comparator of brigatinib and ceritinib.

To demonstrate the additional benefit of brigatinib as a monotherapy of ALK-positive, advanced NSCLC in patients previously treated with crizotinib, the pharmaceutical company presented results from comparisons of individual arms of the ALTA and ASCEND-5 studies.

In the main analysis, the pharmaceutical company compares the authorisation compliant brigatinib arm of the ALTA study and the ceritinib arm of the ASCEND-5 study using a Matching Adjusted Indirect Comparison (MAIC). In a sensitivity analysis, both study arms are also naïvely compared with each other.

The ALTA study is a two-arm open phase II RCT that included patients with ALK-positive, locally advanced, or metastatic NSCLC previously treated with crizotinib who were also eligible for pre-treatment with chemotherapy. The 222 patients were randomised 1:1 to receive brigatinib treatment in either the non-authorisation compliant dose of 90 mg/day or the authorisation compliant dose of 90 mg/day for 7 days followed by 180 mg/day. In the present comparisons, the pharmaceutical company considers the 110 patients who were assigned to the authorisation compliant brigatinib arm.

The ASCEND-5 study is a two-arm open phase III RCT that included patients with ALK-positive, locally advanced, or metastatic NSCLC who were previously treated with crizotinib and one or two chemotherapies (including ≥ 1 platinum-based chemotherapy) according to inclusion criteria. A total of 231 patients were randomly assigned to their treatment at a ratio of 1:1. This consisted either of ceritinib 750 mg/day (on an empty stomach) or chemotherapy (pemetrexed or docetaxel). In the present comparisons, the pharmaceutical company takes into account the 115 patients of the ceritinib arm, who received 750 mg/day of ceritinib on an empty stomach; this no longer corresponds to the authorised dose. The authorised dose of ceritinib was reduced from 750 mg/day (on an empty stomach) to 450 mg/day (taken at mealtime) in April 2018 because this reduces the occurrence of adverse gastrointestinal events.

In the main analysis, the pharmaceutical company used a MAIC to try to align the patient population of the authorisation compliant brigatinib arm from the ALTA study with the patient population of the ceritinib arm from the ASCEND-5 study at the level of aggregated data at the level of individual patient data with regard to selected patient characteristics. Using the resulting patient-individual weights, the pharmaceutical company re-calculates the results for various endpoints for brigatinib for an effective population size of 30.5 of the 110 patients from the authorisation compliant brigatinib arm and compares them with the results of ceritinib arms of the ASCEND-5 study.

In the naïve comparison of the two study arms, the pharmaceutical company calculates the effects between the arms of the two studies as a sensitivity analysis. From the results of a naïve comparison of two studies without considering the structural differences, no statement can be deduced about the additional benefit of brigatinib compared with the appropriate comparator therapy.

The MAIC is afflicted with serious methodological uncertainties, which are explained below. On the basis these, the MAIC is not used for the present benefit assessment:
Overall, the data basis from the MAIC corresponds to an uncontrolled comparison that adjusts for effect modifiers and prognostic factors because of a lack of randomisation.
In the ASCEND-5 study, the patient populations from both studies were aligned on the level of aggregated data generated by extraction of virtual individual patient data (VIPD) from the published Kaplan-Meier curves. Uncertainties result from this procedure because so far, no methodological publications for the combination with IPD and the estimation of VIPD from Kaplan-Meier curves for the MAIC are available. Also for the selection of baseline characteristics, which are used to adapt the patients from the ALTA study to the ASCEND-5 study, there is no methodologically recognised, standardised procedure. The pharmaceutical company identifies 20 baseline characteristics in the dossier but does not describe the criteria for selecting these factors. In the MAIC, there is also no recognised and uniform procedure for estimating the weights of patients. A non-standardised variable selection and weighting of patients entails selection bias and thus the risk of results-driven reporting. In addition, the multicollinearity and the involvement of five clinicians to decide which identified baseline characteristics will be used for adjustment in the MAIC are described in the dossier by the pharmaceutical company. However, the criteria for the selection of clinicians and the exact determination of collinearity cannot be verified on the basis of the information available. It is also not clear why only pairs of multicollinearity studies were carried out. The absence of a bridge comparator in this MAIC further increases the susceptibility to bias described above.
In addition, the ALTA and ASCEND-5 studies show a structural inequality, particularly with regard to previous therapies, with MAIC resulting in an adjustment to a previous therapy

situation that does not reflect the current reality. Thus, in the ASCEND-5 study, more patients were treated with chemotherapy (99.1% and 73.6% in the ASCEND-5 and ALTA studies, respectively), but fewer patients were previously treated with crizotinib (100% and 96.4% in the ASCEND-5 and ALTA studies, respectively). In the MAIC, patients from the ALTA study are adjusted by matching in the direction of the pre-treatment situation with chemotherapy in the ASCEND-5 study. This results in the content-related problem that patients are adjusted to a previous therapy situation with chemotherapy that no longer reflects the current reality with prior TKI treatment. Nevertheless, it should be noted that the planning of a clinical study and the generation of data are fundamentally confronted with the challenge of the high therapeutic dynamics and the associated rapid change in care in terms of previous therapies in the therapeutic indication.
Overall, these serious methodological uncertainties of the MAIC, in particular of the MAIC without bridge comparator, involve a high risk of bias, which is why this comparative methodology is not used for the present benefit assessment.

In support of brigatinib, the pharmaceutical company presents the results of the authorisation compliant brigatinib arms of the ALTA, AP26113-11-101-101, and ALTA-1L studies.

The AP26113-11-101 study is a non-randomised, non-controlled, dose-finding study of brigatinib in 137 adult patients with different tumour entities, 25 of whom are patients of the same therapeutic indication and who received brigatinib at the authorisation compliant dose.
The non-comparative presentation of the respective brigatinib results of the authorisation compliant arm of the ALTA and AP26113-11-101 studies does not result in a comparison with the appropriate comparator therapy. As a result, no statement on the additional benefit of brigatinib compared with the appropriate comparator therapy can be derived from these results.

The ALTA-1L study is an open RCT for the direct comparison of brigatinib versus crizotinib in patients with ALK-positive, locally advanced, or metastatic NSCLC who have not yet been treated with a tyrosine kinase inhibitor. Because of the lack of prior treatment with crizotinib, the patients do not correspond to the target population in the therapeutic indication. In addition, the study investigated brigatinib in comparison to crizotinib. Therefore, no statement on the additional benefit of brigatinib compared with the appropriate comparator therapy can be derived from these results.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the new medicinal product Alunbrig containing the active ingredient brigatinib, which is authorised as a monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.

With the present resolution, the appropriate comparator therapy ceritinib originally determined by the G-BA will be supplemented by alectinib and formulated as follows: “ceritinib or alectinib” This takes into account the hint for a minor additional benefit for alectinib given in the G-BA resolution of 19 October 2017. The current guideline recommendations and the statements of medical societies regarding the therapeutic significance of therapy with alectinib made in the present procedure, which state that alectinib is another standard therapy in the clinical care of patients ALK-positive NSCLC previously treated with crizotinib, have also been taken into account.

There are no direct comparative studies or adjusted indirect comparisons between a common bridge comparator of brigatinib and ceritinib. To demonstrate the additional benefit of brigatinib, results from the authorisation compliant brigatinib arm of the ALTA study and the ceritinib arm of the ASCEND-5 study are presented and compared: On one hand by means of a Matching Adjusted Indirect Comparison (MAIC) in the main analysis and on the other by means of a naïve comparison in a sensitivity analysis.
Because of serious methodological uncertainties, the MAIC is not used for the present benefit assessment. Overall, the data basis from the MAIC corresponds to an uncontrolled

comparison. For decisive methodological steps in MAIC, there are not yet any methodically recognised, standardised procedures (e.g. for the selection of baseline characteristics and estimation of patient weights). Similarly, there are no methodological publications available to date for the alignment of patient populations from both studies at the level of individual patient data (IPD) and virtual individual patient data (VIPD). Furthermore, the criteria for the selection of clinicians and the exact determination of collinearity (in particular the investigation of pairwise multicollinearity) cannot be reconstructed. This results in an overall risk of bias (selection bias) and results-driven reporting, which is further aggravated by the lack of a bridge comparator. In addition, there is the content-related problem that through the MAIC, patients are adjusted to a previous therapy situation with chemotherapy that no longer reflects the current reality with prior TKI treatment.
For the results of the naïve comparison of two studies presented in the sensitivity analysis without considering the structural differences, no statement on the additional benefit of brigatinib compared with the appropriate comparator therapy can be derived.
As supporting evidence of brigatinib, the results of the authorisation compliant brigatinib arms of the ALTA, AP26113-11-101-101, and ALTA-1L studies are presented. The non-comparative presentation of the brigatinib results from the ALTA and AP26113-11-101 studies does not result in a comparison with the appropriate comparator therapy, which is why no statement can be made on the additional benefit of brigatinib compared with the appropriate comparator therapy. Because the patients in the ALTA-1L study did not correspond to the patients in the target population in the present therapeutic indication (because of the lack of prior treatment with crizotinib) and were treated with crizotinib in the control arm, no statement can be derived from these results on the additional benefit of brigatinib compared with the appropriate comparator therapy.

Because there are no data for an assessment of the additional benefit, the additional benefit of brigatinib as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib is not proven.

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

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

The resolution is based on the information on patients for whom treatment with docetaxel or pemetrexed or ceritinib is considered from the resolution of the Federal Joint Committee on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V on alectinib of 19 October 2017.

2.3 Requirements for a quality-assured application

The requirements of 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 Alunbrig® (active ingredient: brigatinib) at the following publicly accessible link (last access: 8 May 2019):
https://www.ema.europa.eu/documents/product-information/alunbrig-epar-product-information_de.pdf

Treatment with brigatinib 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 advanced bronchial carcinoma.

ALK verification

The ALK-positive NSCLC status should be known before initiating treatment with Alunbrig.

A validated ALK test is necessary to identify patients with ALK-positive NSCLC (see Section 5.1). The ALK-positive NSCLC status should be determined by laboratories with proven experience in the specific technique required.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 June 2019).

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 varies from patient to patient and/or is shorter on average.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs. Initial induction schemes are not taken into account in the cost representation.

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				
Brigatinib	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Ceritinib	continuously, 1 × daily	365	1	365
Alectinib	continuously, 2 x daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Brigatinib	Day 1–7: 90 mg from Day 8: 180 mg	90–180 mg	1 × 90 – 180 mg	365	7 × 90 mg + 358 × 180 mg
Appropriate comparator therapy					
Ceritinib	450 mg	450 mg	3 × 150 mg	365	1095 × 150 mg
Alectinib	600 mg	1200 mg	8 × 150 mg	365	2920 × 150 mg

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
Medicinal product to be assessed					
Brigatinib 90 mg	7 PFS	€1,418.16	€1.77	€77.91	€1,338.48
Brigatinib 180 mg	28 PFS	€7,333.08	€1.77	€415.52	€6,915.79
Appropriate comparator therapy					
Ceritinib	90 HC	€5,504.20	€1.77	€0.00	€5,502.43
Alectinib	224 HC	€5,976.57	€1.77	€338.05	€5,636.75
Abbreviations: FCT = film-coated tablets, HC = hard capsules					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 June 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 the standard expenditure in the course of the treatment are not shown.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

Other SHI services: not applicable

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 10 July 2018.

On 15 January 2019, the pharmaceutical company submitted a dossier for the benefit assessment of brigatinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 15 January 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 brigatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 15 January 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 April 2019. The deadline for submitting written statements was 6 May 2019.

The oral hearing was held on 27 May 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 statements received and the oral hearing were discussed at the session of the subcommittee on 24 June 2019, and the proposed resolution was approved.

At its session on 4 July 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 July 2018	Determination of the appropriate comparator therapy
Working group Section 35a	14 May 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 May 2019	Conduct of the oral hearing
Working group Section 35a	4 June 2019 18 June 2019	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	24 June 2019	Concluding discussion of the proposed resolution
Plenum	4 July 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 July 2019

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

Prof Hecken