Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Amivantamab (lung cancer, non-small cell, activating EGFR Exon 20 insertion mutations, after platinum-based chemotherapy)

of 7 July 2022

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient amivantamab 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 2022. 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 14 January 2022.

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 19 April 2022, 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 amivantamab compared to 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 amivantamab.

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 Amivantamab (Rybrevant) in accordance with the product information

Rybrevant as monotherapy is indicated for treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based therapy.

Therapeutic indication of the resolution (resolution of 07.07.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based chemotherapy, for whom further chemotherapy is indicated

Appropriate comparator therapy:

- Docetaxel

or

- Docetaxel in combination with nintedanib

or

- Pemetrexed

b) Adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based chemotherapy, for whom no further chemotherapy is indicated

Appropriate comparator therapy:

- Best supportive care

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

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. In terms of authorisation status, the cytostatic agents cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine and vinorelbine, the protein kinase inhibitors afatinib, erlotinib, gefitinib, nintedanib and osimertinib, and the antibodies atezolizumab, nivolumab, pembrolizumab and ramucirumab are available for the treatment of advanced NSCLC.

Medicinal products for the treatment of NSCLC with ALK translocations and BRAF, RET or ROS1 mutations were not considered here according to the therapeutic indication.

on 2. A non-medicinal treatment option is not considered for the therapeutic indication in question.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Durvalumab (locally advanced, after chemoradiotherapy): resolution of 04.04.2019
- Atezolizumab (NSCLC): resolution of 16.03.2018
- Pembrolizumab (NSCLC, after chemotherapy): resolution of 02.02.2017
- Afatinib (NSCLC, squamous histology): resolution of 20.10.2016
- Nivolumab (NSCLC, non-squamous histology): resolution of 20.10.2016
- Osimertinib (NSCLC with EGFR mutation): resolutions of 15.09.2016, 19.10.2017
- Ramucirumab (NSCLC): resolution of 01.09.2016
- Nivolumab (NSCLC): resolution of 04.02.2016
- Afatinib (NSCLC with EGFR mutation): resolution of 05.11.2015
- Nintedanib (NSCLC): resolution of 18.06.2015

Guidelines:
Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (off-label use): Carboplatin-containing medicinal products for advanced non-small cell lung cancer (NSCLC) - combination therapy

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

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

Among the approved active ingredients listed under 1., only certain active ingredients will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

Therapies explicitly indicated for squamous histology were not considered since EGFR-positive tumours usually have a non-squamous histology.

The present therapeutic indication includes patients with advanced non-small cell lung cancer (NSCLC) and EGFR Exon 20 insertion mutation after platinum-based therapy for whom further chemotherapy is indicated and patients for whom no further chemotherapy is indicated.

a) Patients for whom further chemotherapy is indicated

For patients in whom another antineoplastic therapy is indicated after platinum-based first-line chemotherapy, the cytotoxic chemotherapeutic agents docetaxel and pemetrexed as well as docetaxel in combination with nintedanib are available on the basis of the available evidence.

With docetaxel and pemetrexed, both as monotherapy, two established chemotherapeutic agents are available for second-line chemotherapy, although pemetrexed is not indicated for predominantly squamous histology. For the combination of docetaxel and nintedanib, which is indicated for adenocarcinoma histology, an indication of a minor additional benefit was identified in the benefit assessment compared to docetaxel monotherapy (resolution of 18 June 2015). In the guidelines, docetaxel in combination with nintedanib is recommended alongside the other chemotherapy options, but is not regularly preferred over them. Based on the available evidence, docetaxel and pemetrexed, each as monotherapy, as well as docetaxel in combination with nintedanib, are considered therapeutically comparable, subject to tumour histology and the different side effect profile.

According to the statement of the scientific-medical societies from the present benefit assessment procedure, the same recommendations apply for second-line therapy as for patients without options for another targeted molecular therapy. In this regard, in addition to the chemotherapies already mentioned above, immune checkpoint inhibitors (atezolizumab, nivolumab, pembrolizumab (for PD-L1 expression of >1%) after chemotherapy alone and the combination of the angiogenesis inhibitor ramucirumab with docetaxel are also recommended in second-line therapy.

According to the currently valid S-3 guideline as of February 2018, patients with rare EGFR Exon 20 insertion mutations should be treated like EGFR wild-type patients. Specific treatment options are not mentioned. The recommendation is based on consensus among experts. In the background information, the S-3 guideline states that the first and second-generation TKIs are ineffective for Exon 20 insertions and should not be used. Specific substances that also lead to effective inactivation of the mutated EGFR in EGFR Exon 20 insertions are currently being tested in studies.

For the determination of the appropriate comparator therapy for the present resolution on the benefit assessment, the significance of the immune checkpoint inhibitors (atezolizumab, nivolumab, pembrolizumab (for PD-L1 expression of >1%)) in the treatment specifically of NSCLC with EGFR Exon 20 insertion mutations is currently considered by the G-BA as not yet sufficiently assessable. The fact that the evidence for the use of immune checkpoint inhibitors is limited overall for EGFR mutations without targeted prior therapy is also considered here. Against this background, the immune checkpoint inhibitors are not determined as an appropriate comparator therapy for the present resolution on the benefit assessment.

For the angiogenesis inhibitor ramucirumab in combination with docetaxel, no additional benefit was shown in the benefit assessment compared to docetaxel (resolution of 1 September 2016). Ramucirumab is therefore not considered as an appropriate comparator therapy.

In the overall assessment, the G-BA determined docetaxel, docetaxel in combination with nintedanib and pemetrexed as equally appropriate comparator therapies for patients for whom further chemotherapy is indicated. The additional benefit can be demonstrated compared to one of the therapy options mentioned.

In the course of further development of the generally recognised state of medical knowledge, the significance of the treatment options in the present therapeutic indication may change, which may require a reassessment of the appropriate comparator therapy in the foreseeable future.

b) Patients for whom no further chemotherapy is indicated

The present therapeutic indication includes patients for whom no further chemotherapy is indicated and thus treatment with docetaxel, docetaxel in combination with nintedanib or pemetrexed is not considered. This applies in particular to patients for whom further cytotoxic chemotherapy is not an option due to a deteriorated general condition (these may be in particular patients with ECOG performance status 4, 3 and possibly 2). Best supportive care is determined as the appropriate comparator therapy for this patient group as no specific standard therapy has been established for it according to the current state of medical knowledge. Best Supportive Care (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based chemotherapy, for whom further chemotherapy is indicated

An additional benefit is not proven.

b) Adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based chemotherapy, for whom no further chemotherapy is indicated

An additional benefit is not proven.

Justification:

a) Adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based chemotherapy, for whom further chemotherapy is indicated

To demonstrate an additional benefit of amivantamab compared to the appropriate comparator therapy, the pharmaceutical company submitted a comparison of individual arms from different studies in the dossier in the absence of a direct comparator study and an adjusted indirect comparison via a bridge comparator. These are data on amivantamab from the CHRYSALIS study and, for the appropriate comparator therapy, patient-individual data from the Clinical Research Platform into molecular Testing, Treatment and Outcome of (non-)small Cell Lung Carcinoma Patients (CRISP) registry and the National Network Genomic Medicine (nNGM) Lung Cancer Research Platform registry.

Data source for the intervention with amivantamab: CHRYSALIS study

The CHRYSALIS study is an ongoing, open-label, non-randomised, multicentre study. Adults with histologically or cytologically confirmed metastatic or unresectable NSCLC were enrolled in the study. The patients must have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1.

The CHRYSALIS study is divided into two parts. In the 1st part (dose escalation) of the study, the recommended phase II dose of amivantamab as monotherapy is to be determined in the relevant arm. The 2nd part (dose expansion) of the study aims to assess the safety, tolerability and anti-tumour activity of amivantamab as monotherapy in the arms relevant for the benefit assessment.

For part 2 of the study, patients must have measurable disease according to Response Evaluation Criteria In Solid Tumours (RECIST) criteria version 1.1. Patients in part 2 of the study are included in one of 7 cohorts depending on their mutational status or their prior therapy. Patients receive either amivantamab as monotherapy (cohorts A-D, MET-1 and MET-2) or amivantamab + lazertinib (cohort E).

For the assessment of the additional benefit of amivantamab, the pharmaceutical company considers all patients from part 1 and 2 of the CHRYSALIS study with EGFR Exon 20 insertion mutations after failure of platinum-based therapy, who received an approved dose of amivantamab as monotherapy. These patients received amivantamab intravenously according to the requirements in the product information. Patients were treated until disease progression, unacceptable toxicity or therapy discontinuation as decided by the doctor or patient.

The pharmaceutical company considers different evaluation populations for the benefit assessment. For efficacy endpoints, 114 patients who were enrolled in the study till 04.06.2020 and either had ≥ 3 follow-up visits after the start of the study or discontinued therapy for any reason (including disease progression or death) were evaluated (data cut-off from 30.03.2021). The population for the evaluation on the endpoints for side effects comprises 153 patients who received at least 1 dose of the study medication (regardless of the date of enrolment in the study). For the endpoint of overall mortality, an additional population of 10 study participants who were enrolled in the study after 04.06.2020 was included.

Data source for the appropriate comparator therapy

The pharmaceutical company uses the CRISP and nNGM registries for the appropriate comparator therapy and 16 RCTs in the extended therapeutic indication of NSCLC for evaluations of side effects.

CRISP registry study

CRISP is an ongoing, open-label, non-interventional, prospective, clinical registry study involving about 150 study sites in Germany. The registry collects data on molecular testing, treatment and disease progression of patients with NSCLC and small cell lung cancer (SCLC). According to the information provided by the pharmaceutical company, primary and secondary endpoints include overall survival, response, disease progression, time to subsequent therapy and adverse events. In the course of the cooperation with the registry operator, according to the pharmaceutical company, a prospective survey on safety and tolerability data was started from 29.04.2021 for the sub-population evaluated in the present benefit assessment.

For the present benefit assessment, the pharmaceutical company uses a cohort of the CRISP registry, which contains 7 patients with NSCLC and EGFR Exon 20 insertion mutation after failure of platinum-based therapy. These patients had to fulfil the inclusion criteria of the CHRYSALIS study and had to have been treated with the appropriate comparator therapy, whereby several treatment regimens could be used in the patients during the observation and the patients were included in the analysis several times if necessary. For the CRISP registry study, the pharmaceutical company submits the data cut-off from 30.06.2021.

nNGM registry study

nNGM is an ongoing, open-label, prospective registry study with retrospective data collection. It was founded in 2010 through a cooperation of the University Hospital Cologne with over 300 regional hospitals and medical practices. The registry specialises in the molecular pathological diagnosis of patients with lung cancer and collects both molecular and clinical data. Primary and secondary endpoints include overall survival, response, disease progression, time to subsequent therapy and adverse events.

Patients with NSCLC and EGFR Exon 20 insertion mutation after failure of platinum-based therapy are included in the benefit assessment; they had to fulfil the inclusion criteria of the CHRYSALIS study and had to have been treated with the appropriate comparator therapy.

It was possible to use several treatment regimens for the patients during the observation, which meant that they were included in the analysis several times if necessary. For the nNGM registry study, the data cut-off from 08.07.2021 is presented in the dossier.

RCTs in the extended NSCLC therapeutic indication for endpoints on side effects

Since only information with limited significance on safety and tolerability is available within the scope of the registry studies used, the pharmaceutical company conducts a supplementary information search for RCTs and non-randomised controlled studies with the appropriate comparator therapy in the therapeutic indication NSCLC, irrespective of the presence of an EGFR mutation (NSCLC with EGFR wild-type, any EGFR mutation or unclear EGFR status). In its supplementary information gathering, the pharmaceutical company identifies 16 RCTs and draws on individual arms of these studies for a descriptive comparison with the CHRYSALIS study.

For this purpose, the pharmaceutical company assumes that adverse events occur independently of the mutational status during treatment with a specific medication and that, in the absence of data on the specific mutation, the side effects in similar therapeutic indications can therefore be used.

Assessment:

Selection of patient populations and handling of missing data

The registries lack data on the severity of patient characteristics that were used by the pharmaceutical company for the selection of the patient population in the registry studies and were also partly identified as relevant confounders. If information on these criteria is missing in the registries, the pharmaceutical company assumes values in the normal range and includes these patients in its evaluations. A selection of the patient populations on the basis of an assumption of norm values is not adequate, as it is largely unclear how many patients in the registry studies fulfil the applied inclusion and exclusion criteria purely on the basis of the assumption of norm values and were therefore included in the analyses presented. In addition, due to the lack of information, it is not possible to assess the extent to which the active ingredients defined by the G-BA as appropriate comparator therapy were administered in accordance with the product information and guidelines.

Identification and completeness of the confounders

The inclusion criteria for identifying confounders are not appropriate with regard to the endpoints and the year of publication and may lead to an incompleteness of the relevant confounders. In addition, the confounders identified as relevant by the pharmaceutical company are not completely present in the present data set.

On the RCTs in the extended NSCLC therapeutic indication for endpoints on side effects

Data on side effects from other therapeutic indications of NSCLC cannot be transferred per se to the present therapeutic indication. As the comparison was inadequately processed, it is unclear whether the patient populations of the 16 RCTs used for the comparison show sufficient similarity to the patients of the CHRYSALIS study with Exon 20 insertion mutation. In addition, the purely descriptive comparison of results on adverse events from different studies is not suitable for the benefit assessment, as it does not allow valid comparative statements on side effects.

Comparative data only for patient-relevant endpoint of overall survival

Irrespective of the shortcomings described so far, there are only comparator data for the patient-relevant endpoint of overall survival in the present therapeutic indication. A weighing of benefit and harm within the framework of the benefit assessment is therefore not possible on the basis of the data presented. Furthermore, the effects on the endpoint of overall survival are not large enough that they cannot be explained exclusively by systematic risk of bias in the present data situation.

Overall assessment:

The indirect comparisons presented only yield results on overall survival, but not on other patient-relevant endpoints. Furthermore, the effects on the endpoint of overall survival are not large enough that they cannot be explained exclusively by systematic risk of bias in the present data situation.

Due to relevant uncertainties resulting from the identification and completeness of the confounders, missing data on patient characteristics and their impact on the formation of the evaluated patient populations and on the adjustment of the confounders, the indirect comparison presented in the dossier is not suitable for the assessment of the additional benefit of amivantamab.

Overall, the remaining uncertainties are so serious that the comparisons presented cannot be used for the benefit assessment. Regardless of this, results for only one patient-relevant endpoint are not sufficient.

Overall, the data submitted by the pharmaceutical company are not suitable for the benefit assessment and do not allow an adequate comparison of amivantamab with the appropriate comparator therapy.

The G-BA concludes that there is no evidence of an additional benefit for amivantamab for the treatment of patients with advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy who are eligible for further chemotherapy compared to the appropriate comparator therapy.

Amivantamab may represent a relevant treatment option in specific cases in the present therapeutic indication.

b) Adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based chemotherapy, for whom no further chemotherapy is indicated

An additional benefit is not proven.

Justification:

No data for an assessment of the additional benefit of amivantamab compared to the appropriate comparator therapy were submitted with the dossier by the pharmaceutical company.

Amivantamab may represent a relevant treatment option in specific cases in the present therapeutic indication.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Rybrevant with the active ingredient amivantamab.

This medicinal product was approved under special conditions.

The therapeutic indication assessed here is as follows:

"Rybrevant as monotherapy is indicated for treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based therapy."

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

a) Adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based chemotherapy, for whom further chemotherapy is indicated

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

Docetaxel or docetaxel in combination with nintedanib or pemetrexed.

b) Adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based chemotherapy, for whom no further chemotherapy is indicated

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

Best supportive care.

Assessment in patient group a)

For the benefit assessment, the pharmaceutical company submitted the results from the CHRYSALIS study for the treatment with amivantamab. This is an uncontrolled study and therefore, does not include a comparator group. In the absence of a direct comparator study, an indirect comparison with individual arms from different studies was submitted by the pharmaceutical company. Apart from the fact that this only yields results on overall survival, but not on other patient-relevant endpoints, the remaining uncertainties are so serious that the indirect comparison cannot be used for the benefit assessment. Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of amivantamab in adults with advanced NSCLC and activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy, in whom further chemotherapy is indicated after first-line therapy, is not proven.

Amivantamab may represent a relevant treatment option in specific cases in the present therapeutic indication.

Assessment in patient group b)

For this patient group, no data are available for the assessment of the additional benefit. An additional benefit is not proven.

Amivantamab may represent a relevant treatment option in specific cases in the present therapeutic indication.

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 patient numbers derived by the pharmaceutical company in the dossier are an underestimate.

This is due in particular to the exclusion of patients with locally advanced unresectable carcinoma who were diagnosed in the previous year, the exclusion of patients who have already received therapy at an earlier stage and who suffer from disease progression, and lower percentage values for activating EGFR mutations.

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 Rybrevant (active ingredient: amivantamab) at the following publicly accessible link (last access: 3 May 2022):

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

Treatment with amivantamab should only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of adult patients with non-small cell lung cancer, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and other doctors from specialist groups participating in the Oncology Agreement.

This medicinal product was authorised under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

EGFR Exon 20 insertion mutation testing

Prior to a therapy with Rybrevant, positive EGFR Exon 20 insertion mutational status must be detected using a validated test method.

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 2022).

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

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The treatment costs for best supportive care are different for each individual patient. Because best supportive care has been determined as an appropriate comparator therapy, this is also

reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

For dosages depending on body weight or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[2]

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The annual treatment costs shown refer to the first year of treatment.

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				
Amivantamab	Month 1: 1 x every 7 days From month 2: 1 x per 14-day cycle	28.1	1	28.1
Appropriate comparator therapy				
Patient population a)				
Docetaxel				
Docetaxel	1 x per 21 day cycle	17.4	1	17.4
Docetaxel in combination with nintedanib				
Docetaxel	1 x per 21 day cycle	17.4	1	17.4
Nintedanib	2 x daily on day 2-21 of a 21-day cycle	17.4	20	348
Pemetrexed				
Pemetrexed	1 x per 21 day cycle	17.4	1	17.4

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Patient population b)				
Best supportive care	Different from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Amivantamab	1,050 mg	1,050 mg	3 x 350 mg	28.1	84.3 x 350 mg
Appropriate comparator therapy					
Patient population a)					
Docetaxel					
Docetaxel	75 mg/m^2 = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Docetaxel with nintedanib					
Docetaxel	75 mg/m^2 = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Nintedanib	200 mg	400 mg	4 x 100 mg	348	1,392 x 100 mg
Pemetrexed					
Pemetrexed	500 mg/m^2 = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Patient population b)					
Best supportive care	Different from patient to patient				

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Amivantamab 350 mg	1 CIS	€ 1,847.14	€ 1.77	€ 102.20	€ 1743.17
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Docetaxel 80 mg	1 CIS	€ 415.86	€ 1.77	€ 19.20	€ 394.89
Nintedanib 100 mg	120 SC	€ 2,761.26	€ 1.77	€ 0.00	€ 2,759.49
Pemetrexed 500 mg	1 PIC	€ 266.85	€ 1.77	€ 12.13	€ 252.95
Abbreviations: CIS = concentrate for the preparation of an infusion solution, PIC = powder for the preparation of an infusion solution concentrate, SC = soft capsules					

LAUER-TAXE® last revised: 15 June 2022

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.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I to the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

According to the product information of amivantamab, antihistamines, antipyretics and glucocorticoids should be used before the first infusion (week 1, days 1 and 2) in order to reduce the risk for the occurrence of infusion-related reactions. Subsequent doses require the administration of antihistamines and antipyretics.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient or year
Medicinal product to be assessed							
Amivantamab							
Dexamethasone 10 mg[3] 10 mg	5 x 1 ml 5 mg	€ 14.49	€ 1.77	€ 0.27	€ 12.45	2	€ 12.45
Diphenhydramine[3] 25mg - 50mg	20 TAB 50 mg	€ 4.38	€ 0.19	€ 0.20	€ 3.99	26.1	€ 2.60 - € 5.21
Paracetamol[3,4] 650 mg – 1,000 mg	20 TAB 500 mg	€ 1.50	€ 0.07	€ 0.06	€ 1.37	26.1	€ 1.79 - € 3.58
Pemetrexed							
Dexamethasone[3] 2 x 4 mg	100 TAB 4 mg	€ 79.50	€ 1.77	€ 5.40	€ 72.33	52.2	€ 75.51
Folic acid: 350 - 1,000 µg/day[5]	100 x 400 µg TAB	€ 16.70	€ 0.84	€ 2.58	€ 13.28	365	€ 48.47 - € 96.94
Vitamin B12[3] 1,000 µg/day, every 3 cycles	10 x 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.32	€ 6.71	5.8	€ 3.89
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; INF = infusion solution; TAB = tablets							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the

[3] Fixed reimbursement rate

[4] The cost calculation for paracetamol is based on the single dose of 500 mg of the non-divisible tablets available for cost calculation related to a dose range of 500 - 1,000 mg per day, even if a dose range of 650 - 1,000 mg is given in the product information.

[5] The cost calculation for folic acid is based on the single dose of 400 µg of the non-divisible tablets available for cost calculation related to a dose range of 400 - 800 µg per day, even if a dose range of 350 - 1000 µg is given in the product information.

pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 8 December 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 January 2022, the pharmaceutical company submitted a dossier for the benefit assessment of amivantamab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 17 January 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient amivantamab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 April 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 19 April 2022. The deadline for submitting written statements was 10 May 2022.

The oral hearing was held on 23 May 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 28 June 2022, and the proposed resolution was approved.

At its session on 7 July 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	8 December 2020	Determination of the appropriate comparator therapy
Working group Section 35a	10 May 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	23 May 2022	Conduct of the oral hearing
Working group Section 35a	1 June 2022 15 June 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	28 June 2022	Concluding discussion of the draft resolution
Plenum	7 July 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 7 July 2022

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

Prof. Hecken