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 Entrectinib (ROS1-positive, Advanced Non-small Cell Lung Cancer)

of 18 February 2021

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient entrectinib 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 September 2020. 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 August 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 December 2020 on the website of the G-BA (www.g-ba.de), 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 entrectinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the written statements submitted in the written and oral hearing procedure as well as the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative) according to the criteria laid down in

Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of entrectinib.

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

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

2.1.1 Approved therapeutic indication of entrectinib (Rozlytrek) in accordance with the product information

Rozlytrek as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,

− who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and

− who have not received a prior NTRK inhibitor

− who have no satisfactory treatment options

Therapeutic indication of the resolution (resolution of 18 February 2021):

Rozlytrek as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors

– Crizotinib

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.

[1] General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. Because ROS1-positive non-small cell lung cancer does not usually have activating EGFR mutations or and a non-squamous histology, EGFR-specific therapy options as well as therapies explicitly indicated for squamous histology were not considered in determining the appropriate comparator therapy.

So far, entrectinib and crizotinib are the only medicinal products explicitly approved for the treatment of ROS1-positive non-small cell lung cancer. Taking into consideration the aforementioned restrictions with regard to EGRF mutation and histology, medicinal products with the following active ingredients are approved in the present therapeutic indication: cisplatin, docetaxel, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, vinorelbin, alectinib, brigatinib, ceritinib, crizotinib, dabrafenib in combination with trametinib, erlotinib, lorlatinib, nintedanib, atezolizumab, bevacizumab, nivolumab, durvalumab, pembrolizumab, and ramucirumab.

On 2. Non-medicinal treatment is not considered. For the present therapeutic indication, it is assumed that the patients do not have an indication for definitive local therapy. 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 on 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:

- Brigatinib: Resolution of 15 October 2020
- Atezolizumab: Resolutions of 2 April 2020
- Lorlatinib: Resolution of 22 November 2019
- Pembrolizumab: Resolution of 19 September 2019
- Brigatinib: Resolution of 4 July 2019
- Durvalumab: Resolution of 4 April 2019
- Alectinib: Resolution of 21 June 2018
- Alectinib: Resolution of 19 October 2017
- Atezolizumab: Resolution of 16 March 2018
- Ceritinib: Resolution of 1 February 2018
- Dabrafenib: Resolution of 19 October 2017
- Trametinib: Resolution of 19 October 2017

- Pembrolizumab: Resolution of 3 August 2017
- Ceritinib: Resolution of 16 March 2017
- Crizotinib: Resolution of 16 June 2016
- Crizotinib: Resolution of 16 March 2017
- Pembrolizumab: Resolution of 2 February 2017
- Crizotinib: Resolution of 15 December 2016
- Nivolumab: Resolution of 20 October 2016
- Ramucirumab: Resolution of 1 September 2016
- Nintedanib: Resolution of 18 June 2015

Guidelines:

Annex VI to Section K of the Pharmaceuticals Directive – Prescribability of authorised medicinal products in non-approved therapeutic indications (Off-Label-Use):

- Carboplatinum-containing medicinal products for advanced non-small cell lung cancer (NSCLC) – combination therapy

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in this indication.

Relevant guidelines unanimously recommend crizotinib as first-line therapy for patients with ROS1-positive advanced NSCLC. In addition to entrectinib, crizotinib is the only medicinal product that is explicitly approved for the treatment of ROS1-positive non-small cell lung cancer. However, the evidence for crizotinib in the present therapy situation is limited and based on the results of non-comparative studies.

In the benefit assessment, no additional benefit was identified for crizotinib for the treatment of ROS1-positive, advanced non-small-cell lung cancer for non-pretreated patients (resolution of 16 March 2017) because in the overall view, there were no data available that allowed an assessment of the additional benefit of crizotinib compared with the appropriate comparator therapy.

For the other medicinal products approved in principle in the therapeutic indication, the evidence regarding ROS1-positive NSCLC is also limited, and the corresponding treatment options are not or less strongly recommended in guidelines.

Therefore, also taking into consideration the written statements confirming the value of crizotinib in healthcare, the G-BA has determined crizotinib as an appropriate comparator therapy for patients with ROS1-positive, advanced, non-small cell lung cancer who have not been pre-treated with ROS1 inhibitors.

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

2.1.3 Extent and probability of the additional benefit

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

An additional benefit of entrectinib compared with crizotinib is not proven.

Justification:

Data basis:

In the dossier for the benefit assessment, the pharmaceutical company uses the results of the approval study on entrectinib. This is the STARTRK-2 study, which included adult patients with locally advanced or metastatic solid tumours. The pharmaceutical company also additionally presents the single-arm STARTRK-1, ALKA-372-001, and STARTRK-NG studies on entrectinib.

For the appropriate comparator therapy crizotinib, the pharmaceutical company presents data on crizotinib-treated patients from the US cancer database Flatiron Health in the dossier. The pharmaceutical company also includes the single-arm EUCROSS study.

In its written submission, the pharmaceutical company also resubmits analyses on the indirect comparison of entrectinib with crizotinib. Here, the pharmaceutical company presents results of the STARTRK-2 study from the most recent data cut-off.

STARTRK-2

The STARTRK-2 study is a non-controlled, multi-centre Phase II basket study that has been ongoing since November 2015. The study included adult patients with locally advanced or metastatic solid tumours and evidence of NTRK1/2/3, C-ros oncogene 1 (ROS1) or anaplastic lymphoma kinase (ALK) gene rearrangement. With the exception of patients with non-small cell lung cancer (NSCLC), the patients with the corresponding gene rearrangement may not have been previously treated with tyrosine receptor kinase (TRK), ROS1 or ALK inhibitors. For the benefit assessment in the present therapeutic indication, the pharmaceutical company uses the sub-population of patients with ROS1-positive NSCLC who have not yet received an ROS1 inhibitor.

As of the data cut-off of 31 October 2018, 180 patients with ROS-1 positive NSCLC were included in the STARTRK-2 study and treated with entrectinib.

Data cut-offs and evaluation populations of the STARTRK-2 study

The pharmaceutical company presents different data cut-offs and evaluation populations in the dossier for the STARTRK-2 study. The pharmaceutical company uses the two evaluation populations ROS1 EE (ROS1 Efficacy evaluable) and ROS1 SE (ROS1 Safety evaluable) for the benefit assessment. The pharmaceutical company uses the ROS1 EE evaluation population to analyse endpoints of the endpoint categories mortality, morbidity, and health-related quality of life (data cut-off of 1 May 2019: N = 78, and N = 145; see below). The pharmaceutical company uses the ROS1 SE evaluation population to analyse endpoints of the endpoint category side effects (data cut-off of 31 October 2018: N = 180).

For the data cut-off of 1 May 2019, the dossier includes two evaluation populations depending on the enrolment cut-off date (ECOD).

Patients were included in the 1st evaluation population until the ECOD of 30 November 2017 (ROS EE N = 78). Patients were included in the 2nd evaluation population until 31 October 2018 (ROS EE N = 145)

In its written statement, the pharmaceutical company clarified that the evaluation populations for the endpoints include all patients included up to the respective ECOD regardless of whether the patients responded to treatment with entrectinib, discontinued the study, were progressive, or died. The pharmaceutical company justifies the exclusion of patients who were included only after ECOD with sufficient follow-up time for the analysis of the primary endpoint objective response rate. In addition, with the information on patient flow submitted with the submission on the data cut-off of 1 May 2019 (ECOD 31 October 2018), the pharmaceutical company

outlined the reasons for exclusion for the formation of the evaluation populations with corresponding information on the number of patients excluded as a result. With the information subsequently submitted with the written statement, the composition of the evaluation population is thus sufficiently understandable. Nevertheless, it should be noted that regardless of whether the restriction of the evaluation population is appropriate for the primary endpoint, the exclusion of patients for other endpoints such as overall survival is not appropriate.

Pooled analysis STARTRK-2, STARTRK-1, and ALKA372-001

In addition, a pooled analysis of the ROS1 EE (1st evaluation population; N = 78) and ROS1 SE (N = 180) evaluation populations of the STARTRK-2 study and individual additional adult patients with advanced or metastatic ROS1-positive, ROS1 inhibitor-naïve NSCLC of the STARTRK-1 and ALKA372-001 phase I studies is presented by the pharmaceutical company in the dossier. Patients who received a dosage ≥ 600 mg entrectinib were included in the pooled analysis. Against this background, the pooled analyses are not considered further because it is unclear whether patients who received a dosage > 600 mg no compliant with the marketing authorisation were also included in this analysis.

Comparative data

The STARTRK-2 approval study is a non-controlled study. Thus, this study does not include a comparator group to which the results of treatment with entrectinib could be compared.

For the appropriate comparator therapy crizotinib, the pharmaceutical company presents data on crizotinib-treated patients from the US cancer database Flatiron Health in the dossier. This is a retrospective cohort study. The pharmaceutical company also includes the multi-centre, single-arm EUCROSS Phase II study. Only aggregated data are available for the study population of the EUCROSS study. The study included adults with locally advanced or metastatic ROS1-positive NSCLC treated with crizotinib. Pre-treatment with ALK or ROS1 inhibitors was not allowed.

For the indirect comparison of entrectinib with crizotinib, the pharmaceutical company contrasts results from the STARTRK-2 study at the data cut-off of 1 May 2019 (ECOD 30 November 2017; N = 78) with cohort data from the Flatiron Health database (N = 69) using propensity score analysis or analyses from the EUCROSS study (N = 30) using the matching-adjusted-indirect-comparison (MAIC) method. In the dossier, only data on the endpoints overall survival and PFS are presented.

For deriving the additional benefit of entrectinib, the pharmaceutical company primarily uses the results from the comparison with the Flatiron Health database for the endpoints overall survival and PFS. For further endpoints on morbidity and health-related quality of life, only the results of the STARTRK-2 study are presented in the dossier without making a comparison with crizotinib. For the endpoint category side effects, the pharmaceutical company performs a descriptive comparison with crizotinib for selected AEs.

In its written submission, the pharmaceutical company also resubmits analyses on the indirect comparison of entrectinib with crizotinib. Here, the pharmaceutical company contrasts results from the STARTRK-2 study at the data cut-off of 1 May 2019 (ECOD 31 October 2018; N = 145) with cohort data from the Flatiron Health database (N = 69) using propensity score analysis or analyses from the EUCROSS study (N = 30) using the matching-adjusted-indirect-comparison (MAIC) method. In each case, the pharmaceutical company presents only data on the endpoint overall survival.

Assessment

The present benefit assessment procedure is the second assessment of an active ingredient for ROS1-positive, advanced NSCLC.

For the benefit assessment, the pharmaceutical company submits the results from the STARTRK-2 approval study on adult patients with ROS1-positive NSCLC who have not previously received an ROS-1 inhibitor.

The approval study is a non-controlled study and therefore does not include a comparator group. Overall, the evidence for an additional benefit presented by the pharmaceutical company lacks a comparison with the appropriate comparator therapy. Although the pharmaceutical company submitted evaluations of the results of the treatment with entrectinib, only a comparison was made with the appropriate comparator therapy in the endpoint overall survival.

The indirect comparisons on the endpoint overall survival presented in the dossier as well as in the written statement are each a comparison of individual arms from different studies. The results are subject to uncertainty because of the lack of randomisation. An additional benefit can thus be derived only if the effects are sufficiently large. For the indirect comparisons presented, the observed effects are not large enough for them not to be exclusively due to systematic bias. A potential systematic bias in the results is evident against the background that the survival time analyses of crizotinib-treated patients from the Flatiron Health database and the EUCROSS study differ significantly.

In addition, the transferability of the data from the Flatiron Health database to the German healthcare context is questionable because of structural differences in the health care systems. This was also discussed by the commentators.

Summary

For the benefit assessment, the pharmaceutical company submits the results from the STARTRK-2 approval study on adult patients with ROS1-positive NSCLC who have not previously received an ROS-1 inhibitor.

The pharmaceutical company makes only a comparison with the appropriate comparator therapy in the endpoint overall survival. For the indirect comparisons presented, the observed effects are not large enough for them not to be exclusively due to systematic bias.

In addition, an assessment of the additional benefit with regard to the endpoint categories morbidity, quality of life, and side effects compared with the appropriate comparator therapy is not possible on the basis of the present indirect comparison.

Overall, the data presented are not suitable to demonstrate an additional benefit compared with the appropriate comparator therapy crizotinib. An additional benefit of entrectinib as monotherapy in adult patients with ROS1-positive, advanced NSCLC who have not previously received treatment with ROS1 inhibitors is therefore not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of entrectinib in the therapeutic indication ROS1-positive, advanced non-small cell lung cancer has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

Only for the endpoint of overall survival is data from the STARTRK-2 study from the indirect comparison with the appropriate comparator therapy crizotinib available for the present assessment. Further endpoints for the endpoint categories morbidity, health-related quality of life, and side effects are not presented or are presented only descriptively compared with the appropriate comparator therapy.

The pharmaceutical company is planning an open-label randomised controlled Phase 3 study with crizotinib as a comparator.

Against this background, because comparative data for entrectinib compared with the appropriate comparator therapy crizotinib that may be relevant for the assessment of the benefit of the medicinal product are expected for the endpoint categories mortality, morbidity, health-related quality of life, and side effects, it is justified to temporally limit the resolution until further scientific evidence is available for the assessment of the additional benefit of entrectinib in the therapeutic indication ROS1-positive, advanced non-small cell lung cancer.

The limitation allows the expected final results from the MO41552 study to be included in the benefit assessment of the medicinal product according to Section 35a SGB V.

For this purpose, the G-BA considers a limitation of the resolution until 31 December 2027 to be appropriate.

Conditions of the limitation:

For the renewed benefit assessment after the deadline, the results of the analyses expected for the 4th quarter of 2027 on all endpoints used to prove the additional benefit from the MO41552 study starting in April 2021 are to be submitted in the dossier.

For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline proving an additional benefit of entrectinib in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven. The possibility that a benefit assessment for the medicinal product entrectinib can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2, Nos. 2 – 4 VerfO) remains unaffected by this.

The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long. In accordance with Section 3, number 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment for the medicinal product entrectinib shall recommence when the deadline has expired.

2.1.5 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Rozlytrek with the active ingredient entrectinib.

This medicinal product was approved under special conditions.

Rozlytrek is approved as monotherapy for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.

Crizotinib was determined as an appropriate comparator therapy by the G-BA.

For the benefit assessment, the pharmaceutical company submitted the results from the STARTRK-2 approval study for treatment with entrectinib. This is a non-controlled study and therefore does not include a comparator group.

Overall, the data presented are not suitable to demonstrate an additional benefit compared with the appropriate comparator therapy crizotinib. An additional benefit of entrectinib as monotherapy in adult patients with ROS1-positive, advanced NSCLC who have not previously received treatment with ROS1 inhibitors is therefore 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 pharmaceutical company assumes a range of 462–1274 SHI-insured patients in the target population.

The following calculation steps are used to derive the number of patients in the target population:

1) The number of newly diagnosed patients with lung cancer is approx. 61,408 patients (25,411 women and 35,998 men) for the observation year 2020.

2) The proportion of women with NSCLC is approximately 75.2–78.2%. The proportion of men with NSCLC is approximately 79.8–82.5%.

3a) Of these, approximately 60.2–66.5% are women and 60.2–64.2% are men in Stage IIIB/IV at initial diagnosis.

3b) The proportion of patients with NSCLC diagnosed at an earlier stage (I to IIIA) who progress to Stage IV during the course of the disease is approx. 14.0–15.8%.

4) Based on the sum of the patient proportions of 3a and 3b, 1.5–3.7% of patients have ROS1-positive advanced NSCLC in Stage IIIB/IV.

5) Taking into consideration an expected SHI share of patients of 87.7%, there are approximately 462 to 1,274 patients in the SHI target population.

The derivation of the patient numbers in the dossier appears plausible overall; however, it is subject to uncertainties. Overall, a potential underestimation can be assumed for the number of patients stated by the pharmaceutical company.

This is because the approach of the pharmaceutical company neglects those patients who had already had an advanced stage in the previous year but did not receive treatment with ROS1 inhibitors before the year under review (i.e. 2020).

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 Rozlytrek (active ingredient: entrectinib) at the following publicly accessible link (last access: 15 January 2021):

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

Treatment with entrectinib 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 adult patients with non-small cell lung cancer.

A validated test is required for the selection of patients with ROS1-positive NSCLC. ROS1-positive status must be confirmed before initiating therapy with entrectinib.

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

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 February 2021).

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

Treatment duration:

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 different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Entrectinib	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Crizotinib	continuously, 2 × daily	365	1	365

Usage and consumption:

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.

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					
Entrectinib	600 mg	600 mg	3 × 200 mg	365	1095 × 200 mg
Appropriate comparator therapy					
Crizotinib	250 mg	500 mg	2 × 250 mg	365	730 × 250 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					
Entrectinib 200 mg	90 HKP	€ 9,740.41	€ 1.77	€ 553.00	€ 9,185.64
Appropriate comparator therapy					
Crizotinib 250 mg	60 HC	€ 5,425.95	€ 1.77	€ 0.00	€ 5,424.18
Abbreviations: HC = hard capsules					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 February 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

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.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

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

At its session on 12 November 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. At its session on 17 June 2020, the working group Section 35a redefined the appropriate comparator therapy.

On 5 August 2020, the pharmaceutical company submitted a dossier for the benefit assessment of entrectinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 1 September 2020 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 entrectinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 November 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 December 2020. The deadline for submitting written statements was 22 December 2020.

The oral hearing was held on 12 January 2021.

By letter dated 13 January 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by the IQWiG was submitted to the G-BA on 28 January 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and 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 9 February 2021, and the proposed resolution was approved.

At its session on 18 February 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 November 2019	Determination of the appropriate comparator therapy
Working group Section 35a	17 June 2020	Redefinition of the appropriate comparator therapy
Working group Section 35a	5 January 2021	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	12 January 2021 13 January 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 January 2021 2 February 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	9 February 2021	Concluding discussion of the draft resolution
Plenum	18 February 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 18 February 2021

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

Prof. Hecken