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 (Solid Tumours, Histology Independent)

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 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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult and paediatric patients from the age of 12 years with solid tumours that display 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 and who have no satisfactory treatment options

Patient-individual therapy with the selection of

- Best supportive care and
- Surgical resection (which is likely to lead to severe morbidity) for which a patient-individual clinical benefit is expected.

Best supportive care (BSC) is the therapy that ensures the best possible, patient-individual, supportive treatment to alleviate symptoms and improve the quality of life.

[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.

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

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

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

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

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

On 1., 2., and 3.

Apart from entrectinib and larotrectinib, there are no specific medicinal products approved for the treatment of solid tumours with an NTRK gene fusion or other specific treatment options in this regard. In view of the special nature of a tumour-agnostic therapeutic indication, theoretically all medicinal products or non-medicinal treatment options approved for the treatment of locally advanced or metastatic solid tumours, regardless of the NTRK gene fusion status, could be considered for the determination of the appropriate comparator therapy. However, such a procedure does not appear to make sense for the present therapeutic indication, see also 4th. criterion.

On 3.

The following resolution of the G-BA is available on drug therapies in the present therapeutic indication:

- Larotrectinib: Resolution of 2 April 2020

On 4.

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

In addition to entrectinib, the active ingredient larotrectinib is approved in the present therapeutic indication. For larotrectinib, there is a resolution on the benefit assessment according to Section 35a SGB V (resolution of 2 April 2020). For the benefit assessment, the pharmaceutical company submitted evaluations of the results of treatment with larotrectinib but without making a comparison with the appropriate comparator therapy. The evidence presented does not allow a comparison to be made with the appropriate comparator therapy, thus an additional benefit of larotrectinib is not proven. The clinical value of larotrectinib can currently not be assessed. Larotrectinib was therefore not considered in the present determination of the appropriate comparator therapy.

For the treatment of solid tumours with NTRK gene fusion, there are no other approved medicinal products or other specific treatment options apart from entrectinib and larotrectinib. Against the background that this is a new biomarker in cancer therapy,

there is no indication that patients with NTRK gene fusion are currently treated fundamentally differently from patients without or with unknown NTRK gene fusion.

According to the approved therapeutic indication of entrectinib, therapy with entrectinib is considered only for patients for whom no satisfactory therapy options are available. In the product information for entrectinib (Rozlytrek; last revised October 2020), Section 4.4 states in more detail that entrectinib should be used only if there are no satisfactory treatment options (e.g. if no clinical benefit has been shown or if these treatment options have been exhausted).

In addition, the approved therapeutic indication of entrectinib specifies that entrectinib may be used in a condition in which surgical resection is likely to result in severe morbidity. According to the statements made by medical experts in the written statement procedure, this may in particular involve surgical resection that is likely to lead to a functional impairment or a disfiguring result or that includes amputation of extremities.

If this therapy situation is present in a patient in which surgical resection, which is likely to lead to severe morbidity, represents the therapeutic standard for the respective patient-specific stage of disease and treatment, it can be assumed that a patient-individual clinical benefit can be expected from surgical resection. Surgical resection, which is likely to lead to severe morbidity is therefore the appropriate comparator therapy for comparison with entrectinib for certain patient-individual therapy situation in the present therapeutic indication.

For this reason, the G-BA considers patient-individual therapy with a selection of best supportive care and surgical resection, which probably leads to severe morbidity, for which a clinical benefit is to be expected for the individual patient, to be a suitable and appropriate comparator therapy for the present therapeutic indication.

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 the appropriate comparator therapy 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.

With its written statement, the pharmaceutical company submits an indirect comparison of entrectinib with the appropriate comparator therapy for the endpoint overall survival.

In addition, the pharmaceutical company presents results of the STARTRK-NG study in which paediatric patients with solid tumours with NTRK gene fusion are included in the written statement.

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 NTRK gene fusion.

As of the data cut-off of 31 August 2018, 108 patients with solid tumours with NTRK gene fusion were included in the STARTRK-2 study and treated with entrectinib.

In accordance with the inclusion criteria of the STARTRK-2 study, it is not ensured that only patients “who have no satisfactory treatment options” are included.

STARTRK-NG

The STARTRK-NG study is a Phase I/Ib, non-controlled dose escalation study with subsequent dose extension in paediatric and adult patients up to 22 years of age with relapsed or refractory solid extracranial tumours or primary central nervous system tumours with or without NTRK, C-ros Oncogene 1, or anaplastic lymphoma kinase fusions, which has been ongoing since May 2016. After dose escalation, patients received entrectinib at dosages ranging from 250 to 750 mg/m^2 body surface area.

The pharmaceutical company does not provide information in the dossier or in the written statement for how many paediatric patients with an age ≥ 12 years and an NTRK gene fusion data are available in the STARTRK-NG study. In accordance with the European Public Assessment Report (EPAR), 29 patients were included by 31 October 2018; of these, 7 patients had NTRK gene fusion. These 7 patients were aged between 4 months and 9 years in accordance with EPAR. Thus, the STARTRK-NG study does not include any patients in the present therapeutic indication until 31 October 2018. In addition, analyses were submitted by the pharmaceutical company exclusively for the endpoint tumour response.

NTRK EE and NTRK SE evaluation populations of STARTK-2

In the dossier, the pharmaceutical company primarily uses the two evaluation populations NTRK EE (NTRK efficacy evaluable) and NTRK SE (NTRK Safety evaluable) for the benefit assessment. The NTRK EE analysis population is patients included in the study up to 30 April 2018 (enrolment cut-off date (ECOD)), 6 months before the data cut-off 31 October 2018. Patients who were included only after the ECOD were excluded when forming the NTRK EE analysis population. The pharmaceutical company uses the NTRK EE evaluation population to analyse endpoints of the endpoint categories mortality, morbidity, and health-related quality of life (data cut-off of 31 October 2018: N = 71). The pharmaceutical company uses the NTRK SE evaluation population to analyse endpoints of the endpoint category side effects (data cut-off of 31 October 2018: N = 108).

The evaluation populations comprise a total of 19 (NTRK EE) or 21 (NTRK SE) different tumour entities: secretory salivary gland carcinoma, non-small cell lung cancer, soft tissue sarcoma, primary brain tumour/glioma, breast cancer (non-secretory), secretory breast cancer, colorectal carcinoma, cholangiocarcinoma, carcinoma of the gastro-oesophageal junction, pancreatic cancer, gastrointestinal carcinoma, endometrial carcinoma, ovarian carcinoma, papillary thyroid carcinoma, thyroid cancer (other), neuroblastoma, neuroendocrine tumour, gastrointestinal stromal tumour, cervical adenosarcoma, dedifferentiated chondrosarcoma and follicular dendritic cell sarcoma.

The number of patients per tumour entity and evaluation population, starting from 1 to 12 patients (NTRK EE) or 1 to 16 patients (NTRK SE), varies considerably. For three tumour entities, data of ≥ 10 patients are available for the endpoint categories mortality, morbidity, and

health-related quality of life: Soft tissue sarcoma (N = 11 NTRK EE; N = 13 NTRK SE), non-small cell lung cancer (N = 12 NTRK EE; N = 14 NTRK SE) and secretory salivary gland carcinoma (N = 12 NTRK EE; N = 16 NTRK SE).

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

In addition, a pooled analysis of the evaluation population NTRK EE of the STARTRK-2 study (N = 71) and three further adult patients with solid tumours with an NTRK gene fusion of the phase I studies STARTRK-1 and ALKA372-001, who received a dosage ≥ 600 mg entrectinib is additionally presented by the pharmaceutical company in the dossier (data cut-off of 31 October 2018). However, for this analysis, there are no results available in the dossier for the endpoint category side effects as well as no results separated by tumour entity. The analysis also includes patients who received a dosage > 600 mg, which is not compliant with the marketing authorisation.

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 indirect comparison, the pharmaceutical company presents descriptive historical data for a BSC-treated patient population from a literature search in the dossier for two tumour entities.

In addition, the pharmaceutical company submits an indirect comparison of entrectinib-treated adult patients with the appropriate comparator therapy for the endpoint overall survival in its written statement for the benefit assessment.

The pooled patient population submitted for comparison for treatment with entrectinib includes all patients included in one of the ALKA-372-001 and STARTRK-1 studies or the STARTRK-2 study by 30 April 2018 (ECOD) (clinical cut-off date 31 October 2018).

All patients had a locally advanced or metastatic solid tumour with evidence of NTRK gene fusion and received entrectinib at a dosage ≥ 600mg daily.

For the indirect comparison with the appropriate comparator therapy, the pharmaceutical company uses data from adult patients with an NTRK gene fusion who were treated with a patient-individual therapy other than an NTRK inhibitor from the US Flatiron Health cancer database. The Flatiron Health database contains data from the electronic patient records of cancer patients from oncology clinics in the US. For the comparison, the pharmaceutical company performs a propensity score analysis taking into consideration the factors tumour type, age, time from initial diagnosis to index date (start of therapy in the entrectinib arm or presence of an NTRK-positive test result in the Flatiron Health database), stage at initial diagnosis, and number of previous lines of therapy since advanced disease. The analysis also includes patients who received a dosage > 600 mg, which is not compliant with the marketing authorisation. Information on the treatment of patients in the Flatiron Health database is not available.

Only tumour entities that occurred in both patient populations were considered by the pharmaceutical company for this comparison: cholangiocarcinoma, breast cancer, colorectal carcinoma, endometrial carcinoma, NSCLC, salivary gland carcinoma, and sarcoma.

As a sensitivity analysis, the pharmaceutical company additionally presents results of an indirect comparison without adjustment.

Assessment:

The present benefit assessment procedure is the second assessment of a new oncological medicinal therapy for which the approved therapeutic indication: is not based on (a) specific tumour disease(s) but rather primarily on the detection of a specific gene mutation (here the NTRK gene fusion) independent of the respective tumour entity present. This is a “histology independent” or “tumour-agnostic” therapeutic indication.

According to the current state of knowledge, NTRK gene fusion can be present in numerous tumour entities. On average, the proportion of solid tumours with NTRK gene fusion is quite low. A high prevalence of NTRK gene fusion is known for some rare solid tumour diseases, including papillary thyroid carcinoma, secretory breast carcinoma, and secretory salivary gland carcinoma. The therapeutic indication of entrectinib thus covers different tumour entities and associated tumour diseases with different courses and prognoses.

For the benefit assessment, data on treatment with entrectinib in a total of 21 tumour entities are available from the STARTRK-2 approval study. The number of patients per tumour entity varies greatly (i.e. 1 to a maximum of 16 patients at the latest data cut-off). Data from ≥ 10 patients are available for only three tumour entities:

With regard to the data summarised independently of the tumour entity (NTRK EE, NTRK SE), the main question in the assessment is the extent to which the resulting mean values for the result of treatment with entrectinib can be representative for both the individual tumour entity and the entire spectrum of solid tumours with NTRK gene fusion in the therapeutic indication of entrectinib. The G-BA therefore find a separate consideration of the results per tumour entity to be useful and necessary. However, neither in the dossier nor in the written statement did the pharmaceutical company provide a separate presentation of the results per tumour entity.

However, the evidence for an additional benefit presented by the pharmaceutical company mainly lacks a comparison with the appropriate comparator therapy.

For the indirect comparison, the pharmaceutical company presents historical data for a BSC-treated patient population descriptively for two tumour entities. However, a description of the procedure for the search and selection of the studies is missing. Thus, neither the completeness of the results presented for studies with BSC can be assessed nor can selective reporting be ruled out. In addition, the presentation of the results for the endpoint category side effects is missing. In the written statement, only comparative data for the endpoint overall survival were submitted by the pharmaceutical company for the present assessment. However, also here, these were not separated according to tumour entity.

In accordance with the information of the pharmaceutical company, the evaluations for the endpoint overall survival show no statistically significant difference between entrectinib and a patient-individual therapy. The indirect comparison without adjustment shows a statistically significant difference to the advantage of entrectinib compared with patient-individual therapy. Irrespective of the question to what extent this indirect comparison without adjustment can be suitable for the present assessment, the effects observed are not large enough that they could not come about exclusively through systematic bias in the comparison of individual arms from different studies.

The data on paediatric patients submitted by the pharmaceutical company in the context of the written statement procedure are not suitable for the assessment of the additional benefit in the present therapeutic indication.

It is therefore not possible to assess an additional benefit of entrectinib compared with the appropriate comparator therapy, which is why an additional benefit of entrectinib compared with the appropriate comparator therapy is not proven.

Summary:

For the benefit assessment, the pharmaceutical company presents the results from the STARTRK-2 approval study on adult patients with NTRK gene fusion as well as data on paediatric patients from the STARTRK-NG study on treatment with entrectinib. The therapeutic

indication of entrectinib covers various tumour entities and associated tumour diseases with different courses and prognoses. The G-BA therefore find a separate consideration of the results per tumour entity to be useful and necessary.

Data from the STARTRK-2 study are available for the most recent data cut-off for a total of 21 tumour entities for treatment with entrectinib. The number of patients per tumour entity varies greatly (i.e. 1 to a maximum of 16 patients). Data from ≥ 10 patients are available for only three tumour entities: Soft tissue sarcoma (N = 11 NTRK EE; N = 13 NTRK SE), non-small cell lung cancer (N = 12 NTRK EE; N = 14 NTRK SE) and secretory salivary gland carcinoma (N = 12 NTRK EE; N = 16 NTRK SE).

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 did provide comparative data for the endpoint overall survival, these were not separated by tumour entity.

The data on paediatric patients submitted by the pharmaceutical company are not suitable for assessing the additional benefit in the present therapeutic indication.

The evidence presented does not allow a comparison to be made with the appropriate comparator therapy. Thus, an additional benefit of entrectinib as monotherapy for 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 no satisfactory treatment options is not proven.

2.1.4 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 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

The following therapies were determined as an appropriate comparator therapy by the G-BA: Patient-individual therapy with the selection of

- best supportive care and
- surgical resection (which is likely to lead to severe morbidity) for which a patient-individual clinical benefit is expected.

The present assessment is the second assessment of an oncological medicinal therapy for which the therapeutic indication is based on the detection of a specific gene mutation (here the NTRK gene fusion) and not on a specific tumour disease. This is a “histology independent” or “tumour-agnostic” therapeutic indication.

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. The evidence submitted by the pharmaceutical company does not allow a comparison with the appropriate comparator therapy, which is why an additional benefit of entrectinib is not proven.

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

The number of patients in the present therapeutic indication derived by the pharmaceutical company in the dossier is estimated to be subject to uncertainty.

Thus, patients who were either not yet in a locally advanced or metastatic stage in 2020 or were in a locally advanced or metastatic stage in 2020 and will still be considered after 2021 are not included in the derivation. Furthermore, there is uncertainty about the operationalisation of unsatisfactory therapy options via the presence of at least one second-line therapy as well as the proportion values estimated for this. In addition, the transferability of the range to the proportion value for an NTRK gene fusion is unclear.

In order to enable a consistent consideration of patient numbers in view of these uncertainties, taking into account the most recent resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication, this resolution is based on the relevant information from the resolution on larotrectinib of 2 April 2020. As already stated with regard to the resolution on larotrectinib, the indication of the patient numbers is subject to a high degree of uncertainty and can be both an overestimation and an underestimation.

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: 11 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 experienced in the therapy of adult and paediatric patients with solid tumours, specifically in the treatment of the respective tumour entity, and other physicians of other speciality groups participating in the Oncology Agreement.

Before initiating therapy with entrectinib, the presence of NTRK gene fusion in a tumour sample must be confirmed by a validated test.

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 of entrectinib 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.

Best supportive care:
Because best supportive care has been determined as an appropriate comparator therapy in the context of a patient-individual 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.

Surgical resection:

The therapeutic decision for surgical resection depends on patient-individual factors. Furthermore, the actual costs incurred when performing a surgical resection depend largely on the individual case, including the location of the tumour and the treatment goal. For this reason, the G-BA does not consider it expedient or considers it inappropriate to quantify concrete costs for surgical resection and therefore states that treatment costs are different for each individual patient.

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
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Best supportive care	different for each individual patient			
Surgical resection	different for each individual patient			

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.

For paediatric patients 12 years of age and older, the dosage of entrectinib is 400 mg for a body surface area between 1.11 m^2 and 1.50 m^2 followed by a dosage of 600 mg for a body surface area ≥ 1.51 m^2 according to the product information.

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	Adult patients:				
	600 mg	600 mg	3 × 200 mg	365	1095 × 200 mg
	Paediatric patients from the age of 12 years:				
	300 mg/m²	400 mg – 600 mg	2 × 200 mg – 3 × 200 mg	365	730 × 200 mg – 1095 × 200 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				
Surgical resection	not applicable				

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
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				
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.

For the test to detect NTRK gene fusion, non-quantifiable costs are incurred in the SHI system. Because of the very low average prevalence of NTRK gene fusion in solid tumours, a high number of tests in relation to the number of treatments with entrectinib can be assumed.

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 27 August 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 7 July 2020, the Subcommittee on Medicinal Products 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 2 February 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	27 August 2019	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	7 July 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