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
Entrectinib (new therapeutic indication: solid tumours, neurotrophic tyrosine receptor kinase (NTRK) gene fusion, histology-independent, > 1 month to < 12 years)

of 6 February 2025

**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 all 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 active ingredient entrectinib (Rozlytrek) was listed for the first time on 1 September 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 27 June 2024, entrectinib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 23 July 2024, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient entrectinib with the new therapeutic indication

"Rozlytrek as monotherapy is indicated for the treatment of paediatric patients older than 1 month with solid tumours expressing a neurotropic 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 G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 2024 on the G-BA website (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 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 entrectinib.

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 Entrectinib (Rozlytrek) in accordance with the product information

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients older than 1 month with solid tumours expressing a 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.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

**Therapeutic indication of the resolution (resolution of 06.02.2025):**

Rozlytrek as monotherapy is indicated for the treatment of paediatric patients older than 1 month up to 12 years of age with solid tumours expressing a 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:

Paediatric patients (older than one month up to 12 years of age) 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 and who have no satisfactory treatment options other than larotrectinib

Appropriate comparator therapy for entrectinib as monotherapy:

Individualised therapy with selection of

- larotrectinib
- best supportive care
- surgical resection which is likely to result in severe morbidity, but for which a patient-individual clinical benefit can nevertheless be expected in individual cases

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

On 1., 2. and 3.

In addition to entrectinib, larotrectinib is explicitly approved for this therapeutic indication. Apart from these two active ingredients, there are currently no other specific medicinal products approved for the treatment of solid tumours expressing an NTRK gene fusion or other specific treatment options in this regard.

In view of this special nature of a tumour-agnostic therapeutic indication the appropriate comparator therapy, all medicinal products approved for the treatment of locally advanced or metastatic solid tumours, irrespective of the NTRK gene fusion status, or non-medicinal treatment options could theoretically be considered for the determination of the appropriate comparator therapy.

A research and information on all medicinal products approved for the treatment of solid tumours and other treatment options do not appear to be appropriate. However, an orientating literature research was carried out in relation to the biomarker.

On 2. Surgical resection is considered as a non-medicinal therapy for the treatment of NTRK fusion-positive solid tumours.

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

- Entrectinib (resolution of 18 February 2021)

– Larotrectinib (resolution of 2 April 2020)

On 4. This therapeutic indication is a tumour-agnostic (histology-independent) therapeutic indication in which the histology or type of tumour disease is not specified in further detail.

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

It is clear from the available guidelines for various tumour entities and the written statement of the scientific-medical societies on the question of comparator therapy that treatment with an NTRK inhibitor is a possible treatment option - depending on the tumour entity - for patients with solid tumours with an NTRK gene fusion who have no satisfactory treatment options and who have not received a prior NTRK inhibitor. In addition to entrectinib, the other approved active ingredient larotrectinib is available for this purpose.

There is a resolution on the benefit assessment of larotrectinib according to Section 35a SGB V (resolution of 2 April 2020).

For the benefit assessment, the pharmaceutical company presented evaluations on the results of treatment with larotrectinib, but without making a comparison with the appropriate comparator therapy. Thus, the evidence presented does not allow a comparison with the appropriate comparator therapy, which is why an additional benefit of larotrectinib is not proven.

In the oral hearings of the benefit assessment procedures for larotrectinib and entrectinib (adults and paediatric patients older than 12 years; resolution of 18 February 2021), the clinical experts stated that NTRK inhibitors were not generally preferred over other therapy options such as surgical resection for all tumour entities. This may also involve a surgical resection that is likely to result in functional impairment or a disfiguring resection result, or may involve amputation of extremities. Furthermore, some patients are treated in the sense of best supportive care.

The appropriate comparator therapy is therefore defined as an individualised therapy with selection of larotrectinib, best supportive care and surgical resection, which is likely to lead to severe morbidity, but for which a patient-individual clinical benefit can be expected in specific cases.

"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.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

### 2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

Justification:

The pharmaceutical company did not identify any relevant study for the assessment of the additional benefit of entrectinib in comparison with the appropriate comparator therapy. In this regard, IQWiG did not identify any relevant study in its review of the completeness of the study pool, in line with the information in the dossier. Data that allow an indirect comparison of entrectinib with the determined appropriate comparator therapy are also not available. In the dossier, the pharmaceutical company presents the results of the single-arm label-enabling STARTRK-NG, TAPISTRY and STARTRK-2 studies descriptively for reasons of transparency.

*STARTRK-NG*

The STARTRK-NG study is an ongoing, uncontrolled and open-label study with paediatric patients (birth to < 18 years), which is divided into a dose escalation and an expansion phase. Patients with solid tumours or primary tumours of the central nervous system with or without NTRK1/2/3 or C-ros-oncogene-1 (ROS1) gene fusion in different cohorts were enrolled in the expansion phase. Patients with locally advanced or metastatic tumours and patients for whom surgical tumour resection would probably have led to severe morbidity were able to participate in the expansion phase in the absence of any satisfactory therapy option.

Cohort B enrolled patients with primary tumours of the central nervous system with NTRK1/2/3 or ROS1 gene fusion, cohort D included patients with extracranial solid tumours (including neuroblastomas) with NTRK1/2/3 or ROS1 gene fusion.

By 16 January 2023 (enrolment cut-off date, ECOD), a total of 34 patients were enrolled in cohorts B and D of the STARTRK-NG study. All patients in the study received entrectinib. The treatment with entrectinib was carried out mostly according to the requirements in the product information.

*TAPISTRY*

The TAPISTRY study is an ongoing, uncontrolled, open-label platform study with an umbrella design. Patients with advanced, metastatic or unresectable solid tumours in whom specific oncogenic alteration or a high tumour mutation burden (≥ 13 mutations per megabase) was detected were enrolled in the study. Another requirement was disease progression under previous treatment or previously untreated disease in the absence of an acceptable therapy option. Paediatric patients could be enrolled, depending on the properties of the active ingredient used and the availability of an age-appropriate formulation and dosage recommendation.

A total of 10 patients were enrolled in cohort B (patients (≥ 0 years) with an NTRK1/2/3 gene fusion) until 16 January 2023 (ECOD). All patients in cohort B received entrectinib. The

treatment with entrectinib was carried out mostly according to the requirements in the product information.

*STARTRK-2*

The STARTRK-2 study is an ongoing, uncontrolled, open-label study.

Adult patients with locally advanced or metastatic solid tumours and an NTRK1/2/3, ROS1 or anaplastic lymphoma kinase (ALK) gene fusion were enrolled in the study as part of a basket design. In the dossier, the pharmaceutical company states that neither of the 2 paediatric patients who participated in the study (documented as protocol violation) had an NTRK gene fusion.

Due to the single-arm study design, none of the label-enabling STARTRK-NG, TAPISTRY and STARTRK-2 studies presented descriptively by the pharmaceutical company allows a comparison with the appropriate comparator therapy and are therefore not suitable for the assessment of an additional benefit of entrectinib compared with the appropriate comparator therapy.

In summary, there are no appropriate data for assessment of the additional benefit, which is why an additional benefit of entrectinib for the treatment of paediatric patients older than 1 month with solid tumours expressing NTRK gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, who have not received a prior NTRK inhibitor and who have no satisfactory treatment options, is not proven.

### 2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient entrectinib.

The therapeutic indication assessed here is as follows: "Rozlytrek as monotherapy is indicated for the treatment of paediatric patients older than 1 month up to 12 years of age with solid tumours expressing NTRK gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, who have not received a prior NTRK inhibitor and who have no satisfactory treatment options."

The G-BA determined the appropriate comparator therapy to be an individualised therapy with selection of larotrectinib, best supportive care and surgical resection, which is likely to lead to severe morbidity, but for which a patient-individual clinical benefit can be expected in specific cases.

During the review of the completeness of the study pool, IQWiG did not identify any relevant study in accordance with the information in the dossier. For reasons of transparency, the results of the single-arm label-enabling STARTRK-NG, TAPISTRY and STARTRK-2 studies are presented descriptively by the pharmaceutical company in the dossier.

In summary, no suitable data are available to allow an assessment of the additional benefit, 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 information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the information from the written statement of the pharmaceutical company. This information is subject to uncertainty.

The main reasons for this are the lack of consideration of patients who are either not yet in the locally advanced or metastatic stage in 2024 or are in the locally advanced or metastatic stage in 2024 and die in the same year or are still alive after 2025, as well as underestimated percentages for NTRK gene fusions.

Another reason is the lack of consideration of patients with solid tumours who are not in a locally advanced or metastatic stage, but who have a disease where surgical resection is likely to result in severe morbidity.

## 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: 3 January 2025):

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

Treatment with entrectinib should only be initiated and monitored by specialists in paediatrics and adolescent medicine with a focus on paediatric haematology and oncology who are experienced in the treatment of paediatric patients with solid tumours.

Prior to initiation of treatment with entrectinib, the presence of an NTRK gene fusion in a tumour sample must be confirmed by a validated test.

This medicinal product received a conditional marketing authorisation. 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.

## 2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2025).

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 varies from patient to patient 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 the maximum treatment duration, if specified in the product information.

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

Surgical resection:

The treatment decision in favour of surgical resection, which is likely to result in severe morbidity but for which a patient-individual clinical benefit can be expected in individual cases, depends on patient-individual factors. Furthermore, the actual costs incurred when performing a surgical resection depend largely on the specific case, including the tumour localisation and the treatment objective. For this reason, the G-BA does not consider it expedient or appropriate to quantify specific costs for surgical resection and therefore states that treatment costs are different from patient to patient.

Treatment period:

Paediatric patients (older than one month up to 12 years of age) 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 and who have no satisfactory treatment options other than larotrectinib

| 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 x daily | 365 | 1 | 365 |
| Appropriate comparator therapy | | | | |
| Larotrectinib | Continuously, 2 x daily | 365 | 1 | 365 |
| Best supportive care[2] | Different from patient to patient | | | |
| Surgical resection | Different from patient to patient | | | |

Consumption:

The average body measurements from the KiGGS study[3] were used as the basis for the dosage in relation to the body surface area (BSA) of paediatric patients younger than 1 month. The average body height of paediatric patients older than 1 month is 54.94 cm, the average body weight is 4.2 kg. The average body height of paediatric patients older than 1 month is 55.99 cm, the average body weight is 4.49 kg. This results in an average body surface area of 0.25 $m^2$ (calculated according to Du Bois 1916)[4].

For dosage depending on the BSA of paediatric patients up to the age of 12 years, the average body measurements from the official representative statistics "Microcensus 2021 – body

[2] When comparing entrectinib versus best supportive care, the costs of best supportive care must also be additionally considered for the medicinal product to be assessed.

[3] Reference percentiles for anthropometric measures and blood pressure from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS), www.rki.de

[4] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

measurements of the population" were applied (average body height of 11 to 12-year-olds: 1.50 m; average body weight: 42.1 kg). This results in a body surface area of 1.33 m² (calculated according to Du Bois 1916)[4].

For entrectinib, the lower limit of the specified range corresponds to the dose for paediatric patients older than 1 month recommended in the product information. This amounts to 250 mg entrectinib/ $m^2$ body surface area (BSA) once daily. This is administered in the form of capsules that are prepared as an oral suspension and allow dose increments of 10 mg, with the daily dose to be administered rounded up or down to the nearest 10 mg increment. With a recommended dose of 250 mg/$m^2$ and a BSA of 0.25 $m^2$, the dose to be administered is 62.5 mg, for which a suspension must be prepared from a 100 mg capsule.

For entrectinib, the upper limit of the specified range corresponds to the dosage by body surface area of paediatric patients up to the age of 12 years recommended in the product information. This amounts to 400 mg entrectinib once daily.

The recommended dose of larotrectinib in children and adolescents is 100 mg/$m^2$ twice daily with a maximum of 100 mg per dose. The dose to be administered in paediatric patients aged 1 month and older is 25 mg at a BSA of 0.25 $m^2$.

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.

Paediatric patients (older than one month up to 12 years of age) 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 and who have no satisfactory treatment options other than larotrectinib

| 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 | 250 mg/$m^2$ = 62.5 mg to 400 mg | 60 mg to 400 mg | 1 x 100 mg to 2 x 200 mg | 365 | 365 x 100 mg to 730 x 200 mg |
| Appropriate comparator therapy | | | | | |
| Larotrectinib | 100 mg/m² (max. 100 mg) | 50 mg to 200 mg | 2 x 25 mg to 2 x 100 mg | 365 | 730 x 25 mg to 730 x 100 mg |
| Best supportive care[2] | Different from patient to patient | | | | |
| Surgical resection | Different from patient to patient | | | | |

Costs:

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 Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

**Costs of the medicinal products:**

Paediatric patients (older than one month up to 12 years of age) 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 and who have no satisfactory treatment options other than larotrectinib

| Designation of the therapy | Packaging size | Cost (pharmacy discount price) | Rebate Section 130 SGB V | Rebate Section 130a SGB V | Costs after deduction of statutory rebates |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Entrectinib 100 mg | 30 HC | € 976.04 | € 2.00 | € 53.41 | € 920.63 |
| Entrectinib 200 mg | 90 HC | € 5,669.16 | € 2.00 | € 320.47 | € 5,346.69 |
| Appropriate comparator therapy | | | | | |
| Larotrectinib 25 mg | 56 HC | € 1,394.20 | € 2.00 | € 76.57 | € 1,315.63 |
| Larotrectinib 100 mg | 56 HC | € 5,420.30 | € 2.00 | € 306.26 | € 5,112.04 |
| Abbreviation: HC = hard capsules | | | | | |

LAUER-TAXE® last revised: 1 January 2025

Costs for additionally required SHI services:

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

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services need to be taken into account.

## 2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or

- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Paediatric patients (older than one month up to 12 years of age) 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 and who have no satisfactory treatment options other than larotrectinib

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

References:
Product information for entrectinib (Rozlytrek); Rozlytrek; last revised: June 2024

## 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 11 June 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 23 July 2024, 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 2, sentence 2 VerfO.

By letter dated 31 July 2024 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 entrectinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 October 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2024. The deadline for submitting statements was 22 November 2024.

The oral hearing was held on 9 December 2024.

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 January 2025, and the proposed draft resolution was approved.

At its session on 6 February 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 11 June 2024 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 3 December 2024 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal products | 9 December 2024 | Conduct of the oral hearing |
| Working group Section 35a | 17 December 2024; 14 January 2025 | Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure |
| Subcommittee Medicinal products | 28 January 2025 | Concluding discussion of the draft resolution |
| Plenum | 6 February 2025 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 6 February 2025

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

Prof. Hecken