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 Larotrectinib (Solid Tumours, Histology Independent)

of 2 April 2020

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 larotrectinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 October 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 15 October 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 January 2020, 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 larotrectinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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 larotrectinib.

In the light of the above and taking into account the 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 larotrectinib (Vitrakvi®) in accordance with the product information

VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients 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 no satisfactory treatment options (see sections 4.4 and 5.1).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult and paediatric patients 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 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 clinical benefit is expected for individual patients.

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.

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 5.0 dated 10 July 2017. 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 products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1, 2, and 3

Apart from 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 criterion 4.

On 4.

For the treatment of solid tumours with NTRK gene fusion, there are no other approved medicinal products or other specific treatment options apart from 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 larotrectinib, therapy with larotrectinib is considered only for patients for whom no satisfactory treatment options are available. The product information on larotrectinib (VITRAKVI; last revised September 2019) specifies in Section 4.4 that larotrectinib should be used only if no therapeutic options for which a clinical benefit has been established are available or if these therapeutic options have been exhausted (i.e. no satisfactory therapeutic options). In this therapy situation, best supportive care represents an appropriate comparator therapy.

In addition, the approved therapeutic indication of larotrectinib specifies that larotrectinib may be used in a condition in which surgical resection is likely to result in severe morbidity. According to the information provided in the product information for larotrectinib and 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 patient-specific 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 larotrectinib for certain therapy situations 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

Change of the appropriate comparator therapy:

For the present benefit assessment procedure, the following was originally determined as an appropriate comparator therapy: “Best supportive care”.

The appropriate comparator therapy defined in the present resolution continues to include “best supportive care” as well as the treatment option of surgical resection as part of a patient-individual therapy. Corresponding objections from the written statements are also taken into account.

A renewed benefit assessment because of the change in the appropriate comparator therapy is not required because in the dossier for the benefit assessment, the pharmaceutical company deviates from “best supportive care” as the sole appropriate comparator therapy and instead lists a “patient-individual therapy according to the doctor’s instructions” as an appropriate comparator therapy. The therapy options considered by the pharmaceutical company go in part beyond those mentioned above, but they do include them.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit of larotrectinib 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 pivotal studies on larotrectinib. These are the NAVIGATE, LOXO-TRK-14001, and SCOUT studies in which, depending on the study, adult and/or paediatric patients with metastatic or locally advanced solid tumours were included.

NAVIGATE

The NAVIGATE study is a non-controlled, multi-centre Phase II basket study that has been ongoing since October 2015.

Patients aged 12 years and older with locally advanced or metastasised solid tumours and evidence of NTRK gene fusion who had previously received adequate standard therapy or who were not eligible for such therapy were enrolled in the study. In the basket design, the patients were assigned to different cohorts according to the tumour entity: Non-small cell lung cancer (NSCLC), thyroid carcinoma, soft tissue sarcoma, colorectal carcinoma, salivary gland cancer, bile duct carcinoma, primary tumour of the central nervous system (CNS), other solid tumours

The study included a total of 82 patients treated with larotrectinib as the data cut-off of 30 July 2018.

LOXO-TRK-14001

The LOXO-TRK-14001 study is a non-controlled, multi-centre Phase II dose escalation study that has been ongoing since May 2014.

Adult patients with locally advanced or metastasised solid tumours for whom standard chemotherapy is unsuitable or for whom no standard or curative therapies exist were enrolled in the study.

At the data cut-off of 30 July 2018, the study included 72 patients treated with larotrectinib; with NTRK gene fusion (n = 10), without NTRK gene fusion (n = 62).

SCOUT

The SCOUT study is a non-controlled, multi-centre Phase I dose escalation and expansion study that has been ongoing since December 2015.
Patients aged ≥ 1 month to 21 years with locally advanced or metastatic solid tumours with either relapse, progression, or no response to available therapies or for whom no standard or curative systemic therapies were available were enrolled in the study.
Older patients were enrolled independently of the documented NTRK gene fusion. For patients with infantile fibrosarcoma, no documented evidence was required because of the known high prevalence of NTRK gene fusion in this tumour entity. Furthermore, patients with locally advanced infantile fibrosarcoma were also enrolled if there was the possibility of a potentially curative resection but nonetheless disfiguring surgery or amputation of limbs would have been necessary (neoadjuvant application).
At the data cut-off of 30 July 2018, the study included a total of 54 patients treated with larotrectinib; with NTRK gene fusion (n = 45), without NTRK gene fusion (n = 9).

Evaluation populations ePAS2 and SAS3

In the dossier, the pharmaceutical company primarily uses the two evaluation populations ePAS2 and SAS3 for the benefit assessment.
The ePAS2 evaluation population comprises the pooled data on 93 patients with NTRK gene fusion from the NAVIGATE, LOXO-TRK-14001, and SCOUT studies for the data cut-off of 30 July 2018. With regard to tumour entity, there was no restriction (except for patients with primary CNS tumours); the ePAS2 evaluation population thus comprises 14 different tumour entities: soft tissue sarcoma, salivary gland carcinoma , infantile fibrosarcoma, thyroid carcinoma, lung cancer, melanoma, colorectal carcinoma, gastrointestinal stromal tumour, bone sarcoma, bile duct carcinoma, appendix carcinoma, breast cancer, congenital mesoblastic nephroma, and pancreatic carcinoma.
The number of patients per tumour entity (from 1 to a maximum of 21 patients) varies greatly. Data from ≥ 10 patients are available for four tumour entities: Soft tissue sarcoma (N = 21), salivary gland carcinoma (N = 17), infantile fibrosarcoma (N = 13), thyroid carcinoma (N = 10).
The SAS3 evaluation population presented by the pharmaceutical company includes 9 patients with NTRK gene fusion and primary CNS tumour for the data cut-off of 30 July 2018.

ESMO 2019 evaluation population

In addition, in the dossier, the pharmaceutical company provides supplementary data on an ESMO 2019 evaluation population (N=159) from the data cut-off of 19 February 2019, which was prepared on the occasion of a presentation at the ESMO 2019 congress. However, there are no results separated by tumour entity in the dossier for this evaluation population.

Evaluation populations ePAS4

With the written statement, the pharmaceutical company submits the pooled data from the NAVIGATE, LOXO-TRK-14001, and SCOUT studies for the data cut-off of 15 July 2019. The ePAS4 population comprises data from 164 patients, which is 71 more than ePAS2. In addition, 2 further tumour entities are included (liver carcinoma (N = 1), prostate carcinoma (N = 1)) and cancer of unknown primary aetiology (N = 1). Furthermore, the new data cut-off includes 24 patients with primary tumours in the CNS who are not part of the ePAS4 evaluation population.

There are also clear differences to the new data cut-off with regard to the number of patients per tumour entity (from 1 to a maximum of 36 patients). Data from ≥ 10 patients are available for five tumour entities: Soft tissue sarcoma (N = 36), infantile fibrosarcoma (N = 32), salivary gland carcinoma (N = 27), thyroid carcinoma (N = 21), and lung cancer (N = 13).

The addendum to the benefit assessment of larotrectinib of 13 March 2020 prepared by IQWiG provides information on the results of the new data cut-off from the written statement of the pharmaceutical company; this is broken down by tumour entity.

Comparative data:

All three pivotal studies (NAVIGATE, LOXO-TRK-14001, and SCOUT) are non-controlled studies. Thus, these studies do not include a comparator group to which the results of treatment with larotrectinib could be compared. Likewise, the pooled data submitted by the pharmaceutical company (ePAS2, ePAS 4, primary CNS tumours) do not include a comparator group.

In the dossier, the pharmaceutical company descriptively presents historical data from a literature search for individual tumour entities but does not use them for an indirect historical comparison to prove an additional benefit. The main reasons are that the NTRK gene fusion status is unknown in the historical data and that there is a high heterogeneity in patient and disease characteristics as well as with regard to the therapy situation of the patients, which is why it is also uncertain to what extent the historical data of the therapy situation according to the therapeutic indication of larotrectinib ("for whom no satisfactory therapy options are available") are accurate. Overall, the pharmaceutical company does not consider there to be sufficient comparability of the patient populations for an indirect historical comparison and does not consider it to be significant in the present case.

Assessment:

The present benefit assessment procedure is the first 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 infantile fibrosarcoma, congenital mesoblastic nephroma, secretory breast carcinoma, and secretory thyroid carcinoma. The therapeutic indication of larotrectinib thus covers different tumour entities and associated tumour diseases with different courses and prognoses.

For the benefit assessment, data on treatment with larotrectinib in a total of 17 tumour entities are available from the pivotal studies or the submitted pooled data on patients with NTRK gene fusion (ePAS2, ePAS 4, primary CNS tumours). The number of patients per tumour entity varies greatly (i.e. 1 to a maximum of 36 patients at the latest data cut-off). Data from ≥ 10 patients are available for only five tumour entities:

With regard to the data pooled independently of the tumour entity (ePAS2, ePAS4), the main question in the assessment is the extent to which the resulting mean values for the outcome of treatment with larotrectinib 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 larotrectinib. 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. In this respect, data on demographic and clinical characteristics of the patients, separated according to tumour entity are missing; these are available only for patients with primary CNS tumours. In addition, there is a lack of information on the median observation time separated by tumour entity, which is particularly relevant for the interpretation of data on overall survival

per tumour entity. Furthermore, not all patient-relevant outcomes were presented separately by tumour entity.

However, the evidence for an additional benefit presented by the pharmaceutical company mainly lacks a comparison with the appropriate comparator therapy. Thus, for the present assessment, no comparative data were presented for the appropriate comparator therapy (neither for the pooled data nor for a consideration of individual tumour entities). The pharmaceutical company submitted evaluations of the results of treatment with larotrectinib but without making a comparison with the appropriate comparator therapy.

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

Summary:

For the benefit assessment, the pharmaceutical company presents the results from the NAVIGATE, LOXO-TRK-14001 and SCOUT pivotal studies as well as pooled data on patients with NTRK gene fusion from these studies for treatment with larotrectinib. The therapeutic indication of larotrectinib 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.

From the pooled data, data on treatment with larotrectinib are available for a total of 17 tumour entities. The number of patients per tumour entity varies greatly (i.e. 1 to a maximum of 36 patients). Data from ≥ 10 patients are available for only 5 tumour entities: Soft tissue sarcoma (N = 36), infantile fibrosarcoma (N = 32), salivary gland carcinoma (N = 27), thyroid carcinoma (N = 21), and lung cancer (N = 13).

All three pivotal studies are non-controlled studies and therefore do not include a comparator group. Likewise, the evaluations presented on the pooled data do 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 treatment with larotrectinib, there was no comparison with the appropriate comparator therapy (neither for the pooled data nor for the data on individual tumour entities).

The evidence presented does not allow a comparison to be made with the appropriate compared therapy. Thus, an additional benefit of larotrectinib as monotherapy for adult and paediatric patients 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 no satisfactory treatment options is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product VITRAKVI with the active ingredient “larotrectinib”.

This medicinal product was approved under special conditions.

Larotrectinib is approved as monotherapy for the treatment of adult and paediatric patients 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 no satisfactory treatment options (see sections 4.4 and 5.1 of the product information).

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 clinical benefit is expected for individual patients.

The present assessment is the first 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 presented the results from the NAVIGATE, LOXO-TRK-14001 and SCOUT pivotal studies as well as pooled data on patients with NTRK gene fusion from these studies for treatment with larotrectinib. All three pivotal

studies are non-controlled studies and therefore do not include a comparator group. Likewise, the evaluations presented on the pooled data do not include a comparator group. Although the pharmaceutical company submitted evaluations of the results of treatment with larotrectinib, there was no comparison with the appropriate comparator therapy (neither for the pooled data nor for the data on individual tumour entities).

Thus, the evidence presented does not allow a comparison to be made with the appropriate comparator therapy, which is by an additional benefit of larotrectinib 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 assessed as very uncertain.

Among other things, in addition to the proper consideration of the prevalence of NTRK gene fusion, the pharmaceutical company makes a further restriction based on an assumed test rate when testing for NTRK gene fusion status; a test rate of 5% (lower limit) to 30% (upper limit) was assumed. In the view of the G-BA, this considerable restriction of the target population is not appropriate because the target population also includes patients in whom an existing NTRK gene fusion has not yet been proven. Moreover, the numerical values for the upper and lower limits of the test rate used are not sufficiently comprehensible. For the purpose of determining the number of patients in this resolution, this step is therefore not taken into account in the derivation.

In the subsequent derivation step – limitation to patients without a satisfactory therapy option – the pharmaceutical company assumes that all patients who tested positive for an NTRK gene fusion can be treated only unsatisfactorily using previous therapy options. The target population is thus not limited any further. In the opinion of the G-BA, this assumption is also inappropriate because the proof of NTRK gene fusion does not regularly mean that no satisfactory therapeutic options are available. Thus, evidence of NTRK gene fusion may well be available at a treatment stage in which satisfactory therapeutic options are available. There is thus no estimate for limiting the number of patients for this step in the derivation.

As a result, the resolution is based on the derivation from the dossier of the pharmaceutical company (leaving out the information on the test rate) in a calculated 392 to 767 patients and a rounded figure of 390 to 770 patients in the SHI target population.

This figure is subject to a high degree of uncertainty and may represent 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 Vitrakvi® (active ingredient: larotrectinib) at the following publicly accessible link (last access: 31 January 2020):
https://www.ema.europa.eu/documents/product-information/vitrakvi-epar-product-information_de.pdf

Treatment with larotrectinib 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 larotrectinib, the presence of NTRK gene fusion in a tumour sample should 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 evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

In individual cases, larotrectinib may be a relevant therapy option.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2020).

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 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

Best supportive care:

The treatment costs for best supportive care are different for each individual patient.

Because best supportive care has been determined as an appropriate comparator therapy 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 can vary from patient to patient.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Larotrectinib	continuously, 2 × 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			

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Larotrectinib	Adult patients:				
	100 mg	200 mg	10 × 20 mg/ml	365	36.5 LSE [2000 mg/100 ml]
	Paediatric patients:				
	100 mg/m² (max. 100 mg)	42 mg to 200 mg	2.1 × 20 mg/ml to 10 × 20 mg/ml	365	12.17 OSL[2] [2000 mg/100 ml] to 36.5 LSE [2000 mg/100 ml]
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				
Surgical resection	not applicable				
Abbreviations: OSL = oral solution					

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, the dosage according to the product information on larotrectinib for children and adolescents is 100 mg/m² body surface but not more than 100 mg per dose. The lower limit is based on the body surface area of a newborn baby. Because the height and weight of newborns vary, a body surface area of 0.21 m² is assumed (50th percentile for age 0.0 months for height: 51 cm; for weight: 3.4 kg), resulting in a dosage of 21 mg larotrectinib per application or 42 mg per patient and treatment day as the lower limit.

For those below limit, the calculation of the average annual consumption shall take into account that a period of 30 days after opening is indicated in the product information for the stability of the solution. At a dose of 42 mg per treatment day, this duration is exceeded. Therefore, a consumption of 1 OSL per 30 days is assumed; this results in an average annual consumption of 12.17 OSL.

[2] Taking into account the shelf life of the solution of 30 days after opening.

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					
Larotrectinib	100 ml OSL	€ 6,623.62	€ 1.77	€ 375.00	€ 6,246.85
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				
Abbreviations: OSL = oral solution					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 March 2020

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 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 larotrectinib 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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 August 2019.

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

By letter dated 15 October 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient larotrectinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 January 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 January 2020. The deadline for submitting written statements was 5 February 2020.

The oral hearing was held on 24 February 2020.

By letter dated 25 February 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 13 March 2020.

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 24 March 2020, and the proposed resolution was approved.

On 2 April 2020, the G-BA resolved by written statement to amend the Pharmaceuticals Directive.

The patient representatives support the resolution.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	27 August 2019	Determination of the appropriate comparator therapy
Working group Section 35a	19 February 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	24 February 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 March 2020 18 March 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	24 March 2020	Concluding discussion of the draft resolution
Plenum	2 April 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 April 2020

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

Prof. Hecken