Gemeinsamer Bundesausschuss

Justification

to 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
Repotrectinib (solid tumours, NTRK gene fusion, ≥ 12 years)

of 16 October 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess 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 studies the pharmaceutical company have 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,
7. number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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 decide on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient repotrectinib on 1 May 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 30 April 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 May 2025 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 repotrectinib 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 have 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 repotrectinib.

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 Repotrectinib (Augtyro) in accordance with the product information

AUGTYRO as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with advanced solid tumours expressing a NTRK gene fusion, and

- who have received a prior NTRK inhibitor, or
- have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted

Therapeutic indication of the resolution (resolution of 16 October 2025):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted

Appropriate comparator therapy for repotrectinib as monotherapy:

Individualised therapy with selection of

- Larotrectinib
- Entrectinib
- Best supportive care

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

b) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor

Appropriate comparator therapy for repotrectinib as monotherapy:

Best supportive care

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.

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

On 1. The active ingredients entrectinib and larotrectinib are explicitly approved for the present 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 indicative 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 also 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”).

All entities and histologies of solid tumours are covered against the background of the tumour-agnostic therapeutic indication. The NTRK gene fusions occur in the various entities with varying degrees of prevalence, meaning that the patients in the therapeutic indication constitute a very heterogeneous patient population. For some tumour entities, there are guideline recommendations specifically for the treatment of patients with NTRK gene fusions. It is clear from them that treatment with an NTRK inhibitor is a possible therapy option - depending on the tumour entity - for patients with solid tumours with an NTRK gene fusion who have no other satisfactory therapy options and who have not received a prior NTRK inhibitor. However, the guidelines do

not recommend using an NTRK inhibitor again if patients have already received an NTRK inhibitor in a previous line of therapy.

For this reason, when determining the appropriate comparator therapy, a distinction is made between two patient groups depending on the pretreatment with an NTRK inhibitor or none. The pretreatment results in different appropriate comparator therapies.

a) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted

In addition to repotrectinib, the approved active ingredients larotrectinib and entrectinib are available for patients with solid tumours expressing an NTRK gene fusion, for whom no other satisfactory therapy options are available apart from NTRK inhibitors and who have not yet received an NTRK inhibitor. For the two active ingredients larotrectinib and entrectinib, resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are also available.

For the benefit assessment of larotrectinib, 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 did not allow a comparison with the appropriate comparator therapy, which is why it was determined that an additional benefit of larotrectinib was not proven (resolution of 2 April 2020).

In the benefit assessment of entrectinib, it was also determined by resolution of 18 February 2021 that an additional benefit was not proven, as the assessment of an additional benefit of entrectinib compared to the appropriate comparator therapy was not possible.

Apart from repotrectinib, entrectinib and larotrectinib, there are currently no other approved medicinal products or other specific treatment options for the treatment of solid tumours with an NTRK gene fusion.

The clinical experts stated during the written statement procedure that treatment of patients in the sense of best supportive care is no longer considered appropriate.

In view of the fact that this is a histology-independent therapeutic indication and that there is evidence for only a few tumour entities, specifically for patients with an NTRK gene fusion, it is nevertheless considered appropriate to continue to designate best supportive care as a therapy option. Since, in accordance with the present area of application, treatment options not targeting NTRK gene fusion provide limited clinical benefit, or have been exhausted, it can be assumed that some of the patients in the therapeutic indication will also be treated in the sense of best supportive care.

An individualised therapy with selection of larotrectinib, entrectinib and best supportive care is therefore determined as the appropriate comparator therapy for

patient group a), i.e. adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted.

b) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor

This therapeutic indication also includes patients who have already been treated with an NTRK inhibitor. There is very little evidence available for this treatment setting and, as already explained above and confirmed by the clinical experts in the written statement procedure, this is a very heterogeneous patient population. In these guidelines, the use of larotrectinib and entrectinib is only recommended if an NTRK inhibitor has not yet been used. This is confirmed according to the statements of the clinical experts in the oral hearing, with the justification that no valid data is available to date.

In addition, the clinical experts confirm best supportive care as an appropriate therapy option in the therapeutic indication as part of the written statement procedure, and explain that further therapy options are available in individual cases following a response to targeted therapy with an NTRK inhibitor. However, the evidence for these cases is extremely limited, particularly against the background of the histology-independent therapeutic indication. Also, no specific recommendations in this regard emerge from the available guidelines.

Therefore, the G-BA determines best supportive care as the appropriate comparator therapy for repotrectinib for the patient group b), i.e. adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor.

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

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

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 repotrectinib is assessed as follows:

a) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted

   An additional benefit is not proven.

b) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor

   An additional benefit is not proven.

Justification for both patient populations:

Data basis:

For the benefit assessment, the pharmaceutical company only presented the results of the ongoing, single-arm, pivotal TRIDENT-1 study (phase 2). The efficacy, safety and pharmacokinetics of repotrectinib are investigated in phase 2. Adults and adolescents 12 years of age and older were enrolled and divided into 6 different cohorts based on their tumour entity (NSCLC or another solid tumour), the gene fusion present (ROS1 or NTRK1-3) and their pretreatment (with or without tyrosine kinase inhibitor, chemotherapy and immunotherapy).

The results of patients with NTRK-positive advanced solid tumours, who have not yet received treatment with an NTRK inhibitor (cohort 5) or who have already received 1 or 2 pretreatments with an NTRK inhibitor (cohort 6) are relevant for this benefit assessment.

In the study, treatment with repotrectinib was carried out without any relevant deviations from the product information.

The primary endpoint of phase 2 of the study is the objective response rate. Secondary endpoints are collected in the categories of mortality, morbidity, health-related quality of life and side effects.

In the dossier, the pharmaceutical company presented data on the label-enabling data cut-off from October 2023.

Assessment

The pharmaceutical company only presented the results of the single-arm TRIDENT-1 study (phase 2). These data are unsuitable for the assessment of the additional benefit for both patient population a) and patient population b), as there is no comparison with the appropriate comparator therapy. An additional benefit of repotrectinib for adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted is therefore not proven. An additional benefit is therefore not proven also for adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor.

2.1.4 Summary of the assessment

This assessment concerns the benefit assessment for the active ingredient repotrectinib. The therapeutic indication assessed here is as follows:

"AUGTYRO as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with advanced solid tumours expressing a NTRK gene fusion, and

- who have received a prior NTRK inhibitor, or
- have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted"

In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted

b) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor

On a)

An individualised therapy with selection of larotrectinib, entrectinib and best supportive care was determined as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company only presented the results of the single-arm TRIDENT-1 (phase 2) study. These data are unsuitable for assessment of the additional benefit, as there is no comparison with the appropriate comparator therapy. An additional benefit of repotrectinib is therefore not proven.

On b)

Best supportive care was determined as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company only presented the results of the single-arm TRIDENT-1 (phase 2) study. These data are unsuitable for assessment of the additional benefit, as there is no comparison with the appropriate comparator therapy. An additional benefit of repotrectinib is therefore not proven.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company. The pharmaceutical company's approach is mathematically comprehensible but results in the following uncertainties in particular:

Firstly, this concerns the transfer of the percentages from the procedure for larotrectinib (resolution of 2 April 2020) and the high uncertainty already identified in the resolution on larotrectinib with regard to the range of patients with advanced solid tumours with an NTRK gene fusion. These percentages were also used as the basis for the resolution on entrectinib (resolution of 18 February 2021). For the present procedure, these percentages represent the total number of patients in both patient populations, although pretreatment with an NTRK inhibitor was not taken into account in the derivation of these percentages. This results in further uncertainties for the present assessment.

In the subsequent derivation step, the patients are divided into the two patient populations a) and b). The pharmaceutical company sets up a mathematical model in this case. To this end, they assume that the number of pretreated patients is calculated by multiplying the number of non-pretreated patients by the percentage of patients receiving an NTRK inhibitor in the first line of therapy and by the percentage of progression after the start of such first-line therapy. In principle, the G-BA take a very critical view of this model. In addition, the percentages used for the model are subject to further uncertainties, which result, among other things, from the derivation of the percentage of patients, who received an NTRK inhibitor in the first line of therapy and from the derivation of the percentage of patients who had progression under first-line therapy.

For the reasons mentioned above, the data on the number of patients used as a basis for the resolution are assessed as very uncertain for both patient population a) and patient population b). There may be an overestimation as well as an underestimation here.

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 Augtyro (active ingredient: repotrectinib) at the following publicly accessible link (last access: 7 October 2025):

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

Treatment with repotrectinib should only be initiated and monitored by specialists experienced in the treatment of adult and paediatric patients with solid tumours, specifically in the treatment of the respective tumour entity, and other doctors from other specialist groups participating in the Oncology Agreement.

Prior to initiation of treatment with repotrectinib, 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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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.

Patients in patient group b) of adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor, receive best supportive care. The treatment costs for best supportive care are different from patient to patient. Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

Treatment period:

a) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Repotrectinib	Day 1 – 14: 1 x daily From day 15: Continuously, 2 x daily	365	1	365
Appropriate comparator therapy				
Larotrectinib	Continuously, 2 x daily	365	1	365
Entrectinib	Continuously, 1 x daily	365	1	365
Best supportive care[2]	Different from patient to patient			

b) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Repotrectinib	Day 1 – 14: 1 x daily From day 15: Continuously, 2 x daily	365	1	365
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

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

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.

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 12 years of age and older. The average body height of paediatric patients 12 years of age and older is 153.27 cm, the average body weight is 44.06 kg. This results in an average body surface area of 1.38 m² (calculated according to Du Bois 1916)[4].

For dosages depending on body weight (BW) or body surface area (BSA) of the adult patients, the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[5].

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

For entrectinib, the upper limit of the specified range corresponds to the dosage by body surface area of adult patients recommended in the product information. This amounts to 600 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 maximum dose to be administered in paediatric patients 12 years of age and older is 100 mg at a BSA of 1.38 m^2.

[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

[5] Federal health reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

a) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted

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					
Repotrectinib	160 mg	Day 1 – 14: 160 mg From day 15: 320 mg	Day 1 – 14: 1 x 160 mg From day 15: 2 x 160 mg	365	716 x 160 mg
Appropriate comparator therapy					
Entrectinib	400 mg to 600 mg	400 mg to 600 mg	2 x 200 mg to 3 x 200 mg	365	730 x 200 mg to 1,095 x 200 mg
Larotrectinib	max. 100 mg	max. 200 mg	2 x 100 mg	365	730 x 100 mg
Best supportive care[2]	Different from patient to patient				

b) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor

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					
Repotrectinib	160 mg	Day 1 – 14: 160 mg From day 15: 320 mg	Day 1 – 14: 1 x 160 mg From day 15: 2 x 160 mg	365	716 x 160 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	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:

a) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Repotrectinib 160 mg	60 HC	€ 10,226.34	€ 1.77	€ 580.74	€ 9,643.83
Appropriate comparator therapy					
Entrectinib 200 mg	90 HC	€ 5,535.37	€ 1.77	€ 312.83	€ 5,220.77
Larotrectinib 100 mg	56 HC	€ 5,420.30	€ 1.77	€ 306.26	€ 5,112.27
Best supportive care[2]	Different from patient to patient				
Abbreviation: HC = hard capsules					

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b) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Repotrectinib 160 mg	60 HC	€ 10,226.34	€ 1.77	€ 580.74	€ 9,643.83
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Abbreviation: HC = hard capsules					

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 had 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 designate 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 have 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 have 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 have 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:

a) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted

   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.

b) Adults and adolescents 12 years of age and older with advanced solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and who have received a prior NTRK inhibitor

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.

2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Augtyro is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV. Approval studies include all studies submitted to the regulatory authority in the authorisation dossier for the assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed.

No information was provided on the number of study participants involved in the clinical studies of the medicinal product in the therapeutic indication under assessment, which were conducted or commissioned by the pharmaceutical company at study sites within the scope of SGB V and/or on the total number of study participants.

Due to the absence of information, it is therefore not possible to determine that the percentage of study participants reached or exceeded the relevance threshold of at least 5 per cent.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant extent within the scope of SGB V.

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 their session on 13 April 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at their session on 28 January 2025.

On 30 April 2025, the pharmaceutical company submitted a dossier for the benefit assessment of repotrectinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 30 April 2025 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 repotrectinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 July 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2025. The deadline for submitting statements was 22 August 2025.

The oral hearing was held on 8 September 2025.

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 7 October 2025, and the proposed draft resolution was approved.

At their session on 16 October 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	13 April 2023	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	28 January 2025	New determination of the appropriate comparator therapy
Working group Section 35a	3 September 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	8 September 2025	Conduct of the oral hearing
Working group Section 35a	17 September 2025 1 October 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	7 October 2025	Concluding discussion of the draft resolution
Plenum	16 October 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 October 2025

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

Prof. Hecken