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
Selpercatinib (reassessment after the deadline: thyroid cancer, RET-mutated, monotherapy, 12 years and older)

of 20 November 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. requirement 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 pass a resolution 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 pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient selpercatinib (Retsevmo) on 30 September 2022. For the resolution of 16 March 2023 made by the G-BA in this procedure, a limitation up to 1 June 2025 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Retsevmo recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 27 May 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 September 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 decision on whether an additional benefit of selpercatinib 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 selpercatinib.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have 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 Selpercatinib (Retsevmo) in accordance with the product information

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC).

Therapeutic indication of the resolution (resolution of 20.11.2025):

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC), first-line therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults and adolescents 12 years and older with advanced medullary RET receptor tyrosine kinase (rearranged during transfection - RET)-mutant thyroid cancer; first-line therapy

Appropriate comparator therapy for selpercatinib as monotherapy:

– Vandetanib

or

– cabozantinib

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

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

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 they determine 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. In addition to selpercatinib, the kinase inhibitors cabozantinib and vandetanib are available for advanced medullary thyroid cancer according to the authorisation status.

On 2. A non-medicinal treatment is unsuitable.

On 3. Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Selpercatinib: resolution of 16 March 2023

- Vandetanib: Resolutions of 05.09.2013 and 06.07.2017
- Cabozantinib: resolution of 22 January 2015

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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. A joint written statement of the German Society for Endocrinology (DGE), the German Society for Haematology and Medical Oncology (DGHO) and the German Society for Nuclear Medicine (DGN) is available.

Among the approved active ingredients listed under 1., only certain active ingredients will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

In determining the appropriate comparator therapies, it was assumed that curative treatment measures and local treatment options are no longer considered.

Furthermore, it was assumed that the patients had an indication for systemic antineoplastic therapy due to their symptomatology and that a "watch-and-wait strategy" was therefore not an option.

Systematic reviews, guidelines and the written statement of scientific-medical societies indicate a high significance of the tyrosine kinase inhibitors cabozantinib and vandetanib in the first-line therapy of patients with medullary thyroid cancer (MTC) with symptomatic or progressive disease without pretreatment with cabozantinib and/or vandetanib. This was confirmed in the joint statement of the scientific-medical societies. It cannot be deduced from the available evidence that one of the two active ingredients should be preferred as a rule. The S3 guideline also recommends that vandetanib should only be used in RET-mutated MTC following reanalysis of the approval study.

Furthermore, the S3 guideline recommends offering the selective RET inhibitor selpercatinib to patients with advanced MTC with significant tumour burden and symptomatic or progressive (according to RECIST) metastatic disease and evidence of an RET variant. However, selpercatinib itself is excluded as an appropriate comparator therapy with regard to the research question of the benefit assessment since the present case concerns the determination of the appropriate comparator therapy for selpercatinib.

In the overall assessment, cabozantinib and vandetanib were thus determined to be equally appropriate comparator therapies for first-line therapy without pretreatment.

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 selpercatinib is assessed as follows:

Adults and adolescents 12 years and older with advanced medullary RET receptor tyrosine kinase (rearranged during transfection - RET)-mutant thyroid cancer; first-line therapy

Indication of a major additional benefit.

Justification:

For the proof of the additional benefit of selpercatinib, the pharmaceutical company presented the results of the LIBRETTO-531 study.

The LIBRETTO-531 study is an ongoing, multicentre, open-label, randomised controlled phase III study comparing selpercatinib with cabozantinib or vandetanib, each as monotherapy. Patients 12 years and older with unresctable, locally advanced and/or metastatic RET-mutant medullary thyroid cancer (MTC) not yet been treated with kinase inhibitors in the advanced or metastatic stage of the disease are being investigated. Furthermore, the study participants had to have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 to 2.

A total of 291 patients were enrolled in the study and randomised in a 2:1 ratio to either treatment with selpercatinib (N = 193) or treatment with cabozantinib or vandetanib (N = 98).

The study was started in February 2020 and is being conducted at 143 study sites in North America, South America, Australia, Asia and Europe.

The present benefit assessment is based on the results of the data cut-off from 11.03.2024.

Results on overall survival as well as the endpoints in the categories of morbidity, health-related quality of life and side effects are available.

Only one patient below 18 years of age was enrolled in the LIBRETTO-531 study.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, there was a statistically significant difference to the advantage of selpercatinib compared to cabozantinib or vandetanib.

The extent of the prolongation achieved in overall survival is assessed as a very significant improvement.

Morbidity

Progression-free survival (PFS)

PFS was operationalised in the LIBRETTO-531 study as the time from randomisation to the first documentation of disease progression or death from any cause, whichever occurred first.

Tumour response was assessed using radiological images according to RECIST version 1.1.

There was a statistically significant difference to the advantage of selpercatinib compared to the control arm.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component of mortality was already assessed as an independent endpoint in the present study via the "overall survival" endpoint. The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST 1.1 criteria).

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology (assessed using EORTC QLQ-C30 and Worst Pain NRS)

In the LIBRETTO-531 study, patients' disease symptomatology was assessed using the EORTC QLQ-C30 and the Worst Pain NRS (numerical rating scale).

For the benefit assessment, the pharmaceutical company submitted evaluations for the time to first deterioration by at least 10 points for the EORTC QLQ-C30 and by at least 2 points for the Worst Pain NRS. These are used as the basis for the present assessment.

EORTC QLQ-C30

For each of the endpoints of fatigue, nausea and vomiting, pain, insomnia, appetite loss and diarrhoea in the EORTC QLQ-C30, there was a statistically significant difference to the advantage of selpercatinib compared to cabozantinib or vandetanib.

In contrast, for the symptom scales of dyspnoea and constipation of the EORTC QLQ-C30, there were no significant differences between the treatment arms.

Worst Pain NRS

For the pain endpoint on the pain scale of Worst Pain NRS, there was a statistically significant difference to the advantage of selpercatinib compared to the control arm.

Health status (assessed by EQ-5D VAS)

The health status is assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. Evaluations of the time to first deterioration by at least 15 points were submitted by the pharmaceutical company and used as a basis for the present assessment.

For the health status endpoint, there was a statistically significant difference to the advantage of selpercatinib compared to cabozantinib or vandetanib.

In the overall assessment, therefore, for the endpoint category morbidity, advantages in health status and symptomatology are seen for the endpoints fatigue, nausea and vomiting, pain, insomnia, loss of appetite and diarrhoea in favour of selpercatinib compared with cabozantinib or vandetanib.

Quality of life

EORTC QLQ-C30

The quality of life of patients is assessed in the LIBRETTO-531 study using the functional scales of the EORTC QLQ-C30 questionnaire.

For the benefit assessment, evaluations of the time to first deterioration by at least 10 points were submitted by the pharmaceutical company and used as the basis for the present assessment.

For all scales of the EORTC QLQ-C30 (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), there was a statistically significant difference to the advantage of selpercatinib compared to cabozantinib or vandetanib.

EORTC-IL19

In addition to the EORTC QLQ-C30, the EORTC-IL19 was used in the LIBRETTO-531 study for the assessment of quality of life.

The EORTC-IL19 corresponds to the physical functioning domain of the EORTC QLQ-C30 in terms of content, but it was surveyed more frequently. The EORTC QLQ-C30 was used to comprehensively assess health-related quality of life, which is why the physical functioning endpoint of the EORTC-IL19 was not used additionally for the benefit assessment.

In the overall assessment, there were therefore only advantages of selpercatinib over cabozantinib or vandetanib in terms of health-related quality of life.

Side effects

Adverse events in total

Adverse events occurred in almost all patients. The results for the endpoint "total adverse events" are only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3), therapy discontinuation due to AEs

For the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs, there were statistically significant advantages of selpercatinib compared to cabozantinib or vandetanib.

Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

In the dossier, the pharmaceutical company only presented descriptive evaluations of the mean score or mean changes in the score compared to baseline over the individual measurement time points, but no analyses comparing the treatment arms. In addition, over the course of the study, there were significant percentages of missing values, which were also different between the two study arms, with a significantly greater decrease in the comparator arm.

For this reason, the results of the PRO-CTCAE cannot be used for the assessment of the additional benefit.

FACT-GP5

In the dossier, the pharmaceutical company submitted evaluations for the endpoint of burden of side effects of the therapy, based on the collection of a single item of the FACT-G questionnaire (item GP5: "I am bothered by side effects of treatment").

The assessment of the burden of side effects of the therapy using this single item alone is considered to be of less significant in terms of content. For the individual patient, it is often indistinguishable whether the burden in the individual case can be attributed to side effects of the therapy or to another cause, such as the symptomatology of the underlying disease. For this reason, it is not possible to conduct a standardised assessment of the burden of side effects of the therapy.

Thus, the evaluations on FACT-GP5 submitted by the pharmaceutical company are not used for the assessment of the additional benefit.

Specific AEs

In detail, the specific adverse events showed statistically significant differences to the advantage of selpercatinib with regard to the endpoints of gastrointestinal disorders (SOC, AEs), diarrhoea (PT, AEs), nausea (PT, AEs), vomiting (PT, AEs), asthenia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), metabolism and nutrition disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), blood and lymphatic system disorders (SOC, severe AEs), stomatitis (PT, AEs), mucosa inflammation (PT, AEs), palmar-plantar erythrodysaesthesia syndrome (PT, AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs).

For the endpoints of dry mouth (PT, AEs) and alanine aminotransferase elevated (PT, severe AEs), there was a statistically significant difference to the disadvantage of selpercatinib in each case.

In the overall assessment of the results on side effects, selpercatinib only showed advantages for serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. In detail, there were predominantly advantages for the specific AEs and only disadvantages for the endpoints of dry mouth and alanine aminotransferase elevated.

Overall assessment

Results from the LIBRETTO-531 study are available for the assessment of the additional benefit of selpercatinib for the first-line treatment of advanced RET-mutant MTC in adults and

adolescents 12 years and older for the comparison with cabozantinib or vandetanib in the endpoint categories of mortality, morbidity, quality of life and side effects.

Only one patient below 18 years of age was enrolled in the LIBRETTO-531 study.

For the overall survival, there was a statistically significant difference to the advantage of selpercatinib compared to cabozantinib or vandetanib. The prolongation achieved in overall survival is assessed as a very significant improvement.

In terms of quality of life, there are only advantages of selpercatinib over the appropriate comparator therapy.

In the morbidity endpoint category, selpercatinib also showed advantages in terms of disease symptomatology and health status (assessed using EORTC QLQ-C30, Worst Pain NRS and EQ 5D-VAS) compared with the appropriate comparator therapy.

For the endpoint category of side effects, only advantages of selpercatinib were identified in the results for SAEs, severe AEs and therapy discontinuation due to AEs. In detail, there were predominantly advantages for the specific AEs.

In the overall analysis of the available results on the patient-relevant endpoints, a previously unachieved major improvement in the therapy-relevant benefit of selpercatinib compared with the appropriate comparator therapy was identified across all endpoint categories and especially in terms of overall survival.

As a result, a major additional benefit of selpercatinib over cabozantinib or vandetanib was identified for the first-line treatment of the advanced RET-mutant MTC in adults and adolescents 12 years and older.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the ongoing, open-label, randomised, multicentre phase III LIBRETTO-531 study.

At the study level, the risk of bias is considered low.

The risk of bias for the endpoints of overall survival and side effects is also rated as low.

For the results of the patient-reported endpoints, the risk of bias is classified as high due to the open-label study design with subjective endpoint survey and the decreasing response to the questionnaire in the course of the study.

Overall, the available data basis is subject to uncertainties. However, these uncertainties are not rated so high as to justify a downgrading of the reliability of data of the overall assessment. In particular, the risk of bias of the endpoint of overall survival is rated as low. In summary, the G-BA therefore derive an indication for the identified additional benefit with regard to the reliability of data (probability of additional benefit).

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient selpercatinib due to the expiry of the limitation of the resolution of 16 March 2023.

This medicinal product received a conditional marketing authorisation in the following therapeutic indication:

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC).

The assessment relates to adults and adolescents 12 years and older with advanced RET-mutant MTC in first-line therapy.

Vandetanib or cabozantinib is determined as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company presented the ongoing, open-label phase III LIBRETTO-531 study for comparing selpercatinib as monotherapy with cabozantinib or vandetanib. Only one patient below 18 years of age was enrolled in the LIBRETTO-531 study.

For overall survival, there was a statistically significant advantage for patients in the intervention arm. The prolongation achieved in overall survival is assessed as a very significant improvement.

In terms of quality of life, there are only advantages of selpercatinib over the appropriate comparator therapy.

In the morbidity endpoint category, selpercatinib also showed advantages in terms of disease symptomatology and health status (assessed using EORTC QLQ-C30, Worst Pain NRS and EQ 5D-VAS) compared with the appropriate comparator therapy.

For the endpoint category of side effects, only advantages of selpercatinib were identified in the results for SAEs, severe AEs and therapy discontinuation due to AEs. In detail, there were predominantly advantages for the specific AEs.

In the overall assessment, the G-BA determined a major additional benefit of selpercatinib, based on the significant or very significant benefits across all endpoint categories.

The reliability of data for the identified additional benefit is classified as an indication.

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 initial resolution on selpercatinib (resolution of 16 March 2023)[2].

These patient numbers represent a better estimate. Although the target population was determined exclusively from newly diagnosed patients with MTC at an advanced setting, the

[2] Benefit assessment procedure D-874 selpercatinib; https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/879/

size of the missing population (patients who are diagnosed with MTC at an early stage and are eligible for the target population due to disease progression) is estimated to be small.

In contrast, the information from the pharmaceutical company's dossier is overestimated. The main reason for this is a methodologically inadequate determination of the prevalence of patients whose tumour is diagnosed at an early stage.

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 Retsevmo (active ingredient: selpercatinib) at the following publicly accessible link (last access: 20 August 2025):

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

Treatment with selpercatinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine, endocrinology and diabetology, specialists in paediatrics and adolescent medicine, all of whom are experienced in the treatment of patients with thyroid cancer, as well as other doctors from other specialist groups participating in the Oncology Agreement.

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 EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

RET testing

The presence of an RET gene fusion (NSCLC and non-medullary thyroid cancer) or mutation (MTC) should be confirmed by a validated test prior to starting treatment with Retsevmo.

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 September 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 is patient-individual 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 for the maximum treatment duration, if specified in the product information.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics “Microcensus 2021 – body measurements of the population” were applied to adults (average body height: 1.72 m;

average body weight: 77.7 kg). This results in a BSA of 1.91 m² (calculated according to Du Bois 1916)[3].

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied to adolescents 12 years of age and older (average body height: 1.53 m; average body weight: 44.1 kg). This results in a BSA of 1.38 m² (calculated according to Du Bois 1916)[4].

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.

Cabozantinib is only approved for adults in the present therapeutic indication.

Treatment period:

Adults and adolescents 12 years and older with advanced medullary RET receptor tyrosine kinase (rearranged during transfection - RET)-mutant thyroid cancer; first-line therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Selpercatinib	Continuously, 2 x daily	730	1	365
Appropriate comparator therapy				
Cabozantinib	Continuously, 1 x daily	365	1	365
Vandetanib	Continuously, 1 x daily	365	1	365

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

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

Consumption:

Adults and adolescents 12 years and older with advanced medullary RET receptor tyrosine kinase (rearranged during transfection - RET)-mutant thyroid cancer; first-line therapy

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					
Selpercatinib Body weight < 50 kg	120 mg	240 mg	2 x 40 mg + 2 x 80 mg	365	730 x 40 mg + 730 x 80 mg
Selpercatinib Body weight ≥ 50 kg	160 mg	320 mg	4 x 80 mg	365	1,460 x 80 mg
Appropriate comparator therapy					
Cabozantinib[5]	140 mg	140 mg	1 x 80 mg + 3 x 20 mg	365	365 x 80 mg + 1,095 x 20 mg
Vandetanib BSA < 1.6 m^2	100 mg/ 200 mg	First year of treatment: Week 1 – 8: Starting dose according to a 7-day schedule: 100 mg - 200 mg 100 mg - 200 mg 100 mg - 200 mg 100 mg From week 9: 200 mg	First year of treatment: Week 1 – 8: 1 x 100 mg/ 2 x 100 mg From week 9: 2 x 100 mg	365	First year of treatment: 698 x 100 mg

[5] Cabozantinib is only approved for use in the therapeutic indication under consideration from the age of 18 years

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Vandetanib BSA < 1.6 m^2	100 mg/ 200 mg	Subsequent year: 200 mg	Subsequent year: 2 x 100 mg	365	Subsequent year: 730 x 100 mg
Vandetanib BSA ≥ 1.6 m^2	200 mg/ 300 mg	First year of treatment: Week 1 – 8: Starting dose according to a 7-day schedule: 200 mg From week 9: 300 mg	First year of treatment: Week 1 – 8: 2 x 100 mg From week 9: 1 x 300 mg	365	First year of treatment: 112 x 100 mg + 309 x 300 mg
		Subsequent year: 300 mg	Subsequent year: 1 x 300 mg	365	Subsequent year: 365 x 300 mg
Vandetanib (Adults)	300 mg	300 mg	1 x 300 mg	365	365 x 300 mg

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.

Costs of the medicinal products:

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					
Selpercatinib 40 mg	168 HC	€ 2,863.93	€ 1.77	€ 160.27	€ 2,701.89
Selpercatinib 80 mg	112 HC	€ 3,799.36	€ 1.77	€ 213.69	€ 3,583.90
Appropriate comparator therapy					
Cabozantinib 20/80 mg (for 28 days)	112 HC	€ 5,502.36	€ 1.77	€ 310.95	€ 5,189.64
Vandetanib 100 mg	30 FCT	€ 2,408.31	€ 1.77	€ 134.25	€ 2,272.29
Vandetanib 300 mg	30 FCT	€ 4,758.96	€ 1.77	€ 268.49	€ 4,488.70
Abbreviations: FCT = film-coated tablets; HC = hard capsules					

LAUER-TAXE® last revised: 15 September 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 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.

<u>Concomitant active ingredient</u>

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:

Adults and adolescents 12 years and older with advanced medullary RET receptor tyrosine kinase (rearranged during transfection - RET)-mutant thyroid cancer; first-line therapy

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 selpercatinib (Retsevmo); product information for Lilly Retsevmo; last revised: April 2025

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 12 July 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 27 May 2025, the pharmaceutical company submitted a dossier for the benefit assessment of selpercatinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

By letter dated 28 May 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 selpercatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 August 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 September 2025. The deadline for submitting statements was 22 September 2025.

The oral hearing was held on 6 October 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 11 November 2025, and the proposed draft resolution was approved.

At their session on 20 November 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 July 2022	Determination of the appropriate comparator therapy
Working group Section 35a	1 October 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	6 October 2025	Conduct of the oral hearing,
Working group Section 35a	15.10.2025; 05.11.2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 November 2025	Concluding discussion of the draft resolution
Plenum	20 November 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 November 2025

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

Prof. Hecken