Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)

Selpercatinib (new therapeutic indication: thyroid cancer, RET fusion-positive, refractory to radioactive iodine, first-line or after prior systemic therapy, ≥ 12 years)

of 7 November 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of all reimbursable medicinal products with new active ingredients.

This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient selpercatinib (Retsevmo) was listed for the first time on 15 March 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 20 July 2023, the pharmaceutical company filed an application for postponement of the date for the start of the benefit assessment procedure for selpercatinib in the therapeutic indication "for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer" according to Section 35a paragraph 5b SGB V.

At its session on 20 July 2023, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the other therapeutic indication of the therapeutic indication covered by the application, at the latest six months after the first

relevant date. The marketing authorisation for the other therapeutic indication covered by the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

On 29 February 2024, selpercatinib received the extension of the marketing authorisation for the therapeutic indication "for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)". The extension of the marketing authorisation for the additional therapeutic indication "for the treatment of adults with advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted" was granted on 29 April 2024. Both extensions of the marketing authorisation are classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 15 May 2024, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient selpercatinib with the therapeutic indication

"Monotherapy for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)".

On 11 February 2021, the active ingredient selpercatinib received the marketing authorisation for the therapeutic indication "Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib". The G-BA adopted a resolution on the benefit assessment of selpercatinib in this therapeutic indication on 2 September 2021.

By the extension of the marketing authorisation of 29 February 2024, this therapeutic indication was replaced by the therapeutic indication

"Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)".

Consequently, the therapeutic indication that has already been subject to benefit assessment (marketing authorisation of 11 February 2021) is excluded from the research question of this benefit assessment procedure.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 August 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a 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 has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed

by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of selpercatinib.

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 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 fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)

Therapeutic indication of the resolution (resolution of 07.11.2024):

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate); first-line therapy.

Retsevmo as monotherapy is indicated for the treatment of adolescents 12 years and older with advanced RET fusion-positive thyroid cancer; after previous therapy with a protein kinase inhibitor.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) <u>Adults and adolescents 12 years and older with advanced RET fusion-positive, radioactive iodine-refractory thyroid cancer, first-line therapy</u>

Appropriate comparator therapy for selpercatinib as monotherapy:

- sorafenib

or

- lenvatinib (for adults only)

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

b) Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer, after previous therapy with a protein kinase inhibitor

Appropriate comparator therapy for selpercatinib as monotherapy:

Patient-individual therapy with selection of:

- sorafenib,
- lenvatinib and
- best supportive care

taking into account prior therapy and general condition.

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. According to the authorisation status, the kinase inhibitors carbozantinib, lenvatinib and sorafenib are available in addition to selpercatinib for advanced differentiated thyroid cancer. The cytostatic agent doxorubicin is approved for advanced and anaplastic thyroid cancer.

On 2. Radiotherapy and radioactive iodine therapy are generally considered as non-medicinal treatments in the present therapeutic indication.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:
- Cabozantinib (resolution of 1 December 2022)
- Lenvatinib (resolution of 15 August 2019)
- Selpercatinib (resolution of 2 September 2021)

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic 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 therapeutic indication according to Section 35a paragraph 7 SGB V (see "Information on appropriate comparator therapy"). There is no written feedback from the scientific-medical societies on the question of comparator therapy.

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

The evidence for the present treatment setting is limited. There are no national guidelines for the treatment of patients with advanced differentiated thyroid carcinoma. Furthermore, no Cochrane reviews are available. Some of the available guidelines do not fulfil the methodological quality criteria, but were taken into account due to the lack of higher-quality evidence.

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

With the extension of the marketing authorisation to this therapeutic indication, both an extension to the first-line therapy of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory

(patient group a) and an extension of the line of therapy after previous therapy to adolescents 12 years and older (patient group b) have taken place. The patient population of adults following prior systemic therapy with sorafenib or lenvatinib - sorafenib and lenvatinib are used on-label exclusively in case of radioactive iodine refractoriness - has already been subject to benefit assessment (resolution of the G-BA of 2 September 2021). A distinction is therefore made between 2 patient groups:

a) Adults and adolescents 12 years and older with advanced RET-positive, radioactive iodine-refractory thyroid cancer, first-line therapy

and

b) Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer, after previous therapy with a protein kinase inhibitor

Anaplastic thyroid cancer:

The present therapeutic indication also includes patients with anaplastic thyroid cancer. Taking into account the very low number of patients with advanced anaplastic thyroid cancer, which is further reduced with regard to the occurrence of RET fusion following prior therapy with sorafenib and/or lenvatinib, no subdivision of the patient population is made with regard to histology.

Patient group a); first-line therapy

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.

The guidelines contain specific therapy recommendations depending on the presence of RET fusion. The active ingredients selpercatinib and pralsetinib are recommended for patients with RET fusion-positivity. Selpercatinib is newly approved in first-line therapy in the therapeutic indication and is the medicinal product to be assessed in this benefit assessment. Pralsetinib is not approved in the present therapeutic indication. The available evidence does not indicate that therapy with pralsetinib is preferable to the current, approved standard therapies in patients with advanced thyroid cancer and RET fusion. Pralsetinib is not determined to be an appropriate comparator therapy.

According to the available evidence, the guidelines recommend the tyrosine kinase inhibitors (TKIs) sorafenib or lenvatinib for first-line therapy of patients with advanced, differentiated thyroid cancer with symptomatic or progressive disease.

The inhibitor lenvatinib is covered by a resolution of 15 May 2019 on the benefit assessment according to Section 35a SGB V, by which it was found that an additional benefit over the appropriate comparator therapy (sorafenib) is not proven. No suitable data were available for this benefit assessment.

The joint statement by the German Society of Endocrinology (DGE) and the German Society for Haematology and Medical Oncology (DGHO) shows that treatment with sorafenib or lenvatinib is in line with current recommendations.

It cannot be deduced from the available evidence that one of the two active ingredients should be preferred as a rule. Thus, lenvatinib and sorafenib were determined to be equally appropriate comparator therapies for first-line therapy of adults.

There is little evidence on treatment options specifically for the treatment of adolescents 12 years and older. The available guidelines for the treatment of advanced, differentiated thyroid cancer recommend consideration of systemic therapy with tyrosine kinase inhibitors. Only the tyrosine kinase inhibitor sorafenib is approved for adolescents. For adolescents 12 years and older, sorafenib is therefore determined to be the appropriate comparator therapy in first-line therapy.

The appropriate comparator therapy determined here includes several therapy options. In this context, individual therapy options only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

Any therapy option that is not restricted by the bracketed patient and disease characteristics can be used for demonstrating the additional benefit for the total population. If the appropriate comparator therapy comprises several therapy option alternatives without any restriction, the additional benefit for the total population can be demonstrated in comparison with one of these therapeutic alternatives; as a rule, this can be done as part of a single comparator study.

In contrast, the sole comparison with a therapy option that only represents a comparator therapy for part of the patient population is generally insufficient to demonstrate the additional benefit for the total population.

Patient group b; adolescents 12 years and older following prior therapy with a protein kinase inhibitor

With regard to the present treatment setting – progression following prior systemic therapy with a protein kinase inhibitor - very little evidence with regard to subsequent therapies is available for both adolescents 12 years and older and adults.

According to the guidelines for adults, selpercatinib or pralsetinib are possible therapy options in the presence of a RET fusion.

In the benefit assessment of selpercatinib in advanced thyroid cancer with existing fusion of the RET receptor tyrosine kinase in adults following sorafenib and/or lenvatinib prior therapy, it was found by resolution of 2 September 2021 that an additional benefit compared to the appropriate comparator therapy (patient-individual therapy with a choice of sorafenib, lenvatinib and best supportive care; taking into account histology, prior therapy and general condition) was not proven, as no suitable data were available for a comparison with the appropriate comparator therapy. Selpercatinib is the medicinal product to be assessed in the present benefit assessment for adolescents 12 years and older.

Pralsetinib is not approved in the therapeutic indication. The available evidence does not indicate that therapy with pralsetinib is preferable to the current, approved

standard therapies in patients with advanced thyroid cancer and RET fusion. Pralsetinib is not determined to be an appropriate comparator therapy.

The guidelines for paediatric patients do not differentiate according to the line of therapy. According to the available evidence,[2,3] the use of protein kinase inhibitors should be considered for adolescents 12 years and older with advanced, differentiated thyroid cancer in the event of disease progression. The studies referenced in the guidelines are based on the active ingredients sorafenib and lenvatinib. Lenvatinib is not approved for adolescents 12 years and older in this therapeutic indication.

In the statements on the benefit assessment of selpercatinib in adult patients (resolution of 2 September 2021), the clinical experts stated that in the reality of care, after treatment with one of the two TKIs sorafenib or lenvatinib, a switch to the other active ingredient is made in the subsequent line if the corresponding prerequisites are met.

The TKI cabozantinib is approved for adults who have undergone prior systemic therapy. For cabozantinib, there is a resolution of 1 December 2022 on the benefit assessment, according to which an additional benefit compared to the appropriate comparator therapy (patient-individual therapy with selection of sorafenib, lenvatinib and best supportive care; taking into account previous therapy and general condition) is not proven. Since cabozantinib is not mentioned in both the guidelines for adolescents and the written statement of the scientific-medical societies, cabozantinib is not determined to be an appropriate comparator therapy.

The therapeutic indication also includes patients with advanced differentiated thyroid carcinoma who are not eligible for a switch to the other TKI due to their disease characteristics. Furthermore, patients are included for whom no further anti-neoplastic therapy options are available after prior systemic therapy. According to the current state of medical knowledge, there is no specific standard therapy for these patients. Treatment is given in a patient-individual manner in the sense of best supportive care. Best supportive care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

Merely best supportive care as comparator therapy for the entire patient population b) according to the present therapeutic indication does not correspond to the generally accepted state of medical knowledge.

In the overall assessment, for patient population b) adolescents 12 years and older following prior therapy with a protein kinase inhibitor, a patient-individual therapy with a choice of sorafenib, lenvatinib and best supportive care, taking into account the prior therapy and the general condition, is therefore determined as the appropriate comparator therapy.

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[2] Howard SR et al. Paediatric differentiated thyroid carcinoma: a UK National Clinical Practice Consensus Guideline. Endocr Relat Cancer 2022;29(11):g1-g33.

[3] Lebbink CA et al. 2022 European Thyroid Association Guidelines for the management of paediatric thyroid nodules and differentiated thyroid carcinoma. Eur Thyroid J 2022;11(6).

For the implementation of patient-individual therapy in a direct comparator study, it is expected that investigators will have a choice of several treatment options that will allow a patient-individual treatment decision to be made, taking into account the criteria mentioned (multi-comparator study). The selection and, if necessary, limitation of treatment options must be justified. The patient-individual treatment decision with regard to the comparator therapy should be made before group allocation (e.g. randomisation). This does not include necessary therapy adjustments during the course of the study (e.g. due to the onset of symptomatology or similar).

If only a single comparator study is presented, the extent to which conclusions can be drawn about a sub-population will be examined as part of the benefit assessment.

<u>On the determination of an off-label use of medicinal products as the appropriate comparator therapy:</u>

For the treatment of adolescents with a protein kinase inhibitor (TKI), the guidelines[2,3] mention the active ingredients sorafenib and lenvatinib as possible therapy options. Lenvatinib is not approved for adolescents in this therapeutic indication. According to the guideline, some of the adolescents may have already been treated with sorafenib and are therefore ineligible for renewed therapy with sorafenib despite suitability for further TKI treatment. In previous benefit assessment procedures in the therapeutic indication "Treatment of previously treated thyroild cancer in adults", the clinical experts stated that, after treatment with the TKI sorafenib or lenvatinib, a switch to the other active ingredient is made in the subsequent line if the corresponding prerequisites are met.[4,5] The off-label use of lenvatinib may therefore be medically necessary for adolescents for whom a renewed therapy with sorafenib is not an option. According to the generally recognised state of medical knowledge in the therapeutic indication to be assessed, the off-label use is therefore considered part of the therapy standard in the medical treatment situation as it would be without the medicinal product to be assessed.

The generally recognised state of medical knowledge points out that the off-label use of lenvatinib for adolescents for whom a renewed therapy with sorafenib is not an option is generally preferable to the medicinal products previously approved in the therapeutic indication in accordance with Section 6, paragraph 2, sentence 3, number 3 AM-NutzenV. In the overall assessment, it is therefore appropriate to determine the off-label use of lenvatinib as part of a patient-individual therapy, taking into account the previous therapy and general condition, as an appropriate comparator therapy for patient group b) in addition to the approved therapy option and best supportive care.

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[2] Howard SR et al. Paediatric differentiated thyroid carcinoma: a UK National Clinical Practice Consensus Guideline. Endocr Relat Cancer 2022;29(11):g1-g33.

[3] Lebbink CA et al. 2022 European Thyroid Association Guidelines for the management of paediatric thyroid nodules and differentiated thyroid carcinoma. Eur Thyroid J 2022;11(6).

[4] Benefit assessment procedure for the active ingredient selpercatinib (D-657), https://www.g-ba.de/bewertungs-verfahren/nutzenbewertung/666/

[5] Benefit assessment procedure for the active ingredient cabozantinib (D-826), https://www.g-ba.de/bewertungs-verfahren/nutzenbewertung/838/

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:

a) Adults and adolescents 12 years and older with advanced RET fusion-positive, radioactive iodine-refractory thyroid cancer, first-line therapy

An additional benefit is not proven.

b) Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer, after previous therapy with a protein kinase inhibitor

An additional benefit is not proven.

Justification:

The pharmaceutical company did not identify any relevant studies to demonstrate an additional benefit of selpercatinib compared to the appropriate comparator therapy. Data that allow an indirect comparison of the active ingredient to be assessed with the appropriate comparator therapy determined in each case are also not available. In the dossier, the pharmaceutical company presented the results of the uncontrolled approval studies LIBRETTO-001 and LIBRETTO-121 as the best available evidence.

LIBRETTO-001 study

The LIBRETTO-001 study is a 2-phase, multicentre, single-arm, prospective basket study that has been ongoing since 2017. In the already completed phase 1, the maximum tolerable dose was determined. In the still ongoing phase 2, the determined dose was applied.

The study was conducted in 84 study sites in 16 countries in Europe, North America, and Asia-Pacific.

The first phase of the study investigated dose escalation in patients 12 years and older with locally advanced or metastatic solid tumours, regardless of RET status and pretreatment, who showed disease progression or were intolerant to previous standard therapies. In phase 2, ill subjects 12 years and older with locally advanced or metastatic solid tumours with RET alteration were enrolled into different cohorts. Until the current 6th data cut-off (presented additionally) from 13.01.2023, a total of 968 patients were enrolled.

Adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate) are relevant for this therapeutic indication. The sub-population relevant for the benefit assessment comprises 18 adult patients who have not yet received any prior therapy apart from radioactive iodine

therapy. For the benefit assessment, the pharmaceutical company presented the 4th data cut-off from 15.06.2021.

Adolescents aged 12 to 18 years with RET fusion-positive thyroid cancer were not enrolled in the LIBRETTO-001 study, regardless of previous therapy.

LIBRETTO-121

The LIBRETTO-121 study is a multicentre, single-arm, prospective basket study that has been ongoing since 2019 and is also being conducted in 2 phases.

The study was conducted in 26 study sites in 11 countries in Europe, North America, Asia and Australia.

In the first phase of the study, dose escalation was also carried out to investigate the maximum tolerated dose, and in the ongoing phase 2, the maximum tolerated dose is being applied in several cohorts.

The LIBRETTO-121 study enrolled patients aged between 6 months and 21 years with locally advanced or metastatic solid tumours or primary tumours of the central nervous system, who showed relapse or progression on available therapies, had not responded to available therapies and had no option of a standard therapy or available curative systemic therapy.

Adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate) are relevant for this therapeutic indication. The sub-population relevant for the benefit assessment comprised 8 patients aged 12 to under 18 years with advanced RET fusion-positive papillary thyroid cancer in first-line therapy. No pretreated adolescents 12 years and older with advanced RET fusion-positive thyroid cancer were enrolled in the LIBRETTO-121 study. To date, only the 1st data cut-off (first interim analysis from 13.01.2023) was performed.

a) <u>Adults and adolescents 12 years and older with advanced RET fusion-positive, radioactive iodine-refractory thyroid cancer, first-line therapy</u>

Due to the single-arm study design, the LIBRETTO-001 and LIBRETTO-121 studies presented by the pharmaceutical company do not allow a comparison with the appropriate comparator therapy and are therefore unsuitable for the assessment of an additional benefit of selpercatinib. There are therefore no suitable data for the assessment of the additional benefit of selpercatinib compared with the appropriate comparator therapy. An additional benefit of selpercatinib as monotherapy for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive, radioactive iodine-refractory thyroid cancer in the first line is therefore not proven.

b) <u>Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer, after previous therapy with a protein kinase inhibitor</u>

No pretreated adolescents 12 years and older with advanced RET fusion-positive thyroid cancer were enrolled in the LIBRETTO-001 and LIBRETTO-121 studies presented by the pharmaceutical company. As a result, no data were presented for the assessment of the additional benefit of selpercatinib over the appropriate comparator therapy for the treatment

of adolescents 12 years and older following prior therapy with a protein kinase inhibitor. Thus, an additional benefit for adolescents 12 years and older with advanced RET fusion-positive thyroid cancer after previous therapy with a protein kinase inhibitor is not proven.

2.1.4 Summary of the assessment

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

Retsevmo received a conditional marketing authorisation.

The therapeutic indication assessed here is as follows:

"Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)."

Selpercatinib is currently being assessed in first-line therapy in adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer that is refractory to radioactive iodine and exclusively in adolescents 12 years and older for patients after prior therapy. The benefit assessment for adults who have undergone sorafenib and/or lenvatinib prior therapy was carried out by resolution of 2 September 2021.

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

a) Adults and adolescents 12 years and older with advanced RET fusion-positive, radioactive iodine-refractory thyroid cancer, first-line therapy

   and

b) Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer, after previous therapy with a protein kinase inhibitor

Patient group a)

Treatment with sorafenib or lenvatinib (lenvatinib for adults only) was determined as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company submitted the results of the LIBRETTO-001 and LIBRETTO-121 studies. Due to the single-arm study design, the LIBRETTO-001 and LIBRETTO-121 studies do not allow a comparison with the appropriate comparator therapy and are therefore unsuitable for the assessment of an additional benefit of selpercatinib. An additional benefit is therefore not proven.

Patient group b)

The appropriate comparator therapy was determined to be a patient-individual therapy, selecting sorafenib, lenvatinib and best supportive care, taking into account the prior therapy and the general condition.

No data were submitted by the pharmaceutical company that would allow an assessment of the additional benefit. An additional benefit 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).

As a starting point, the pharmaceutical company distinguishes between differentiated thyroid carcinomas (DTC) with the subtypes papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and poorly differentiated thyroid carcinoma (PDTC), as well as anaplastic thyroid carcinomas (ATC).

In the derivation of the patient numbers for patient population a) and patient population b) carried out by the pharmaceutical company in the dossier, there are both overestimating and underestimating factors, the extent of which cannot be quantified.

For both patient groups, this is especially due to the consideration of separate percentage ranges for the 4 subtypes of thyroid carcinoma - PTC, FTC, PDTC, ATC - whose upper limits add up to a value of more than 100%.

Further uncertainties regarding the patient numbers with advanced DTC or ATC are based on the operationalisation of the advanced stage via tumour stage III to IV, as the allocation to different stages of the disease depends on age, the exclusion of patients who only progress to an advanced stage during the course of their disease and the exclusion of cases in which the disease progression was only known with the death certificate. The joint calculation of percentages for adults and young people 12 years and older also leads to a lack of clarity.

For the percentage of patients who are refractory to radioactive iodine (patient population a), the percentages for the lower and upper limits are subject to uncertainty. In addition, it is assumed for the DTC that all patients, who are refractory to radioactive iodine (RAI) are eligible for systemic therapy. However, systemic therapy is not always recommended for subjects with asymptomatic, stable disease.

Different sources are used to determine the percentage of different subtypes of thyroid cancer with RET fusion. For all subtypes (patient populations a) and b)), percentages for lower and/or upper limit are subject to uncertainty. Furthermore, a higher percentage of paediatric patients may have a positive RET fusion status compared to adults.

In patient population b), the further derivation refers exclusively to patients with DTC. When converting incidence to prevalence, there is uncertainty regarding the 1-year mortality rate used.

For patients who receive systemic therapy following prior treatment with sorafenib and/or lenvatinib, the following uncertainties exist, which lead to a lack of clarity: the data for the 3rd and 4th lines of therapy do not refer exclusively to the DTC; the data refer exclusively to the metastatic stage (the advanced stage without metastases is not taken into account); the exclusion of patients who have not received therapy but would be eligible for it.

For patient population b), 1.8% is assumed when determining the percentage of adolescent patients in the SHI target population, which relates to all forms of thyroid cancer.

Overall, the patient numbers stated for patient population a) and patient population b) are subject to uncertainty. It cannot be ruled out that the number may be higher especially for the number of adolescents aged 12 to 17 years of age.

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: 15 October 2024):

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 and specialists in paediatrics and adolescent medicine with a focus on paediatric haematology and oncology, all of whom are experienced in the treatment of patients with thyroid cancer, as well as other doctors from 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 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 mutation (MTC) or RET fusion (all other tumour types) should be confirmed by a validated test prior to treatment with Retsevmo.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 2024).

For the cost representation, one year is assumed for all medicinal products. The (daily) doses recommended in the product information were used as the calculation basis.

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

There is no marketing authorisation for lenvatinib for adolescents 12 years and older in this therapeutic indication. In accordance with the guidelines,[6,7] the G-BA uses a range of 20 mg – 24 mg lenvatinib per day as the basis for calculating costs in the context of off-label use for adolescents 12 years and older, whereby the lower limit of the dose range is based on the[7] study by Mahajan et al. (2018)[8] referenced in the guideline.

[6] Howard SR et al. Paediatric differentiated thyroid carcinoma: a UK National Clinical Practice Consensus Guideline. Endocr Relat Cancer 2022;29(11):g1-g33.

[7] Lebbink CA et al. 2022 European Thyroid Association Guidelines for the management of paediatric thyroid nodules and differentiated thyroid carcinoma. Eur Thyroid J 2022;11(6).

[8] Mahajan P, Dawrant J, Kheradpour A, Quintanilla NM, Lopez ME, Orth RC, Athanassaki I & Venkatramani R. Response to Lenvatinib in children with papillary thyroid carcinoma. Thyroid 2018 28 1450–1454.

For patient group a) "Adults and adolescents 12 years and older with advanced RET fusion-positive, radioactive iodine-refractory thyroid cancer, first-line therapy", the lenvatinib label Lenvima approved for this therapeutic indication is used for adults.

Due to the principle of economic efficiency according to Section 12 SGB V, the off-label use of lenvatinib in patient group b) "Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer, after previous therapy with a protein kinase inhibitor" is based on the lenvatinib label Kisplyx or Lenvima, which is identical in terms of the active ingredient and dosage form and more economically favourable in terms of potency.

The treatment costs for best supportive care are different from patient to patient. Because best supportive care for patient group b) has been determined as an appropriate comparator therapy, best supportive care for patient group b) 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 and older with advanced RET fusion-positive, radioactive iodine-refractory 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				
Adults and adolescents aged 12 years and above				
Selpercatinib	Continuously, 2 x daily	365	1	365
Appropriate comparator therapy				
Adults and adolescents aged 12 years and above				
Sorafenib	Continuously, 2 x daily	365	1	365
Adults				
Lenvatinib	Continuously, 1 x daily	365	1	365

b) Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer, after previous therapy with a protein kinase 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				
Adolescents 12 years of age and older				
Selpercatinib	Continuously, 2 x daily	365	1	365
Best supportive care[9]	Different from patient to patient			
Appropriate comparator therapy				
Adolescents 12 years of age and older				
Sorafenib	Continuously, 2 x daily	365	1	365
Lenvatinib	Continuously, 1 x daily	365	1	365
Best supportive care [9]	Different from patient to patient			

Consumption:

The lower limit[8] of the dose range of lenvatinib is 14 mg/m^2/day. For determining the lower limit of the dosage depending on body weight (BW) or body surface area (BSA), the average body measurements of 12-13-year-olds from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.56 m; average body weight: 47.1 kg). This results in a body surface area of 1.44 m² (calculated according to Du Bois 1916)[10].

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.

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

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

a) Adults and adolescents 12 years and older with advanced RET fusion-positive, radioactive iodine-refractory 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					
Adults and adolescents aged 12 years and above					
Selpercatinib	< 50 kg: 120 mg	240 mg	2 x 40 mg + 2 x 80 mg	365	730 x 40 mg + 730 x 80 mg
	≥ 50 kg: 160 mg	320 mg	4 x 80 mg	365	1,460 x 80 mg
Appropriate comparator therapy					
Adults and adolescents aged 12 years and above					
Sorafenib	2 x 400 mg	800 mg	4 x 200 mg	365	1,460 x 200 mg
Adults					
Lenvatinib	24 mg	24 mg	2 x 10 mg + 1 x 4 mg	365	730 x 10 mg + 365 x 4 mg

b) Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer, after previous therapy with a protein kinase 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					
Adolescents 12 years of age and older					
Selpercatinib	< 50 kg: 120 mg	240 mg	2 x 40 mg + 2 x 80 mg	365	730 x 40 mg + 730 x 80 mg
	≥ 50 kg: 160 mg	320 mg	4 x 80 mg	365	1,460 x 80 mg
Best supportive care[9]	Different from patient to patient				
Appropriate comparator 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
Adolescents 12 years of age and older					
Sorafenib	2 x 400 mg	800 mg	4 x 200 mg	365	1,460 x 200 mg
Lenvatinib	14 mg/m² = 20.2 mg – 24 mg	20.2 mg - 24 mg	2 x 10 mg – 2 x 10 mg + 1 x 4 mg	365	730 x 10 mg – 730 x 10 mg + 365 x 4 mg
Best supportive care[9]	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:

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	€ 2.00	€ 160.27	€ 2,701.66
Selpercatinib 80 mg	112 HC	€ 3,799.36	€ 2.00	€ 213.69	€ 3,583.67
Appropriate comparator therapy					
Sorafenib 200 mg	112 FCT	€ 371.26	€ 2.00	€ 17.08	€ 352.18
Lenvatinib 10 mg	30 HC	€ 1,329.12	€ 2.00	€ 72.96	€ 1,254.16
Lenvatinib 10 mg (Lenvima)	30 HC	€ 1,548.19	€ 2.00	€ 85.12	€ 1,461.07
Lenvatinib 4 mg (Lenvima)	30 HC	€ 1,192.69	€ 2.00	€ 65.41	€ 1,125.28
Lenvatinib 10 mg (Kisplyx)	30 HC	€ 1,329.12	€ 2.00	€ 72.96	€ 1,254.16
Abbreviations: FCT = film-coated tablets; HC = hard capsules					

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Costs for additionally required SHI services:

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

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

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

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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

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

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it

can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

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

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

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

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

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

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

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

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

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

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

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

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

a) Adults and adolescents 12 years and older with advanced RET fusion-positive, radioactive iodine-refractory 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: July 2024

b) Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer, after previous therapy with a protein kinase 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.

References:
Product information for selpercatinib (Retsevmo); product information for Lilly Retsevmo; last revised: July 2024

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 12 July 2022, 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 its session on 9 April 2024.

On 15 May 2024, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2, sentence 1 VerfO.

By letter dated 15 May 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient selpercatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 08 August 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 August 2024. The deadline for submitting statements was 5 September 2024.

The oral hearing was held on 23 September 2024.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 29 October 2024, and the proposed draft resolution was approved.

At its session on 7 November 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 July 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	9 April 2024	New determination of the appropriate comparator therapy
Working group Section 35a	17 September 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	23 September 2024	Conduct of the oral hearing
Working group Section 35a	30 September 2024 15 October 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	29 October 2024	Concluding discussion of the draft resolution
Plenum	7 November 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 7 November 2024

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

Prof. Hecken