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:
medullary thyroid cancer, RET-mutated, monotherapy, 12 years and older)

of 16 March 2023

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for 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 online 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 2 September 2022, selpercatinib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 30 September 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient selpercatinib with the new

therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new 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 G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 January 2023 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 (invented name: 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 16 March 2023):
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

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication 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.

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

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:

- Cabozantinib: Resolution of 22 January 2015
- Vandetanib: Resolutions of 5 September 2013 and 6 July 2017

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.

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. Thus, for first-line therapy without pretreatment, cabozantinib and vandetanib were determined to be equally appropriate comparator therapies.

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

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

An additional benefit is not proven.

Justification:

For the proof of an additional benefit of selpercatinib, the pharmaceutical company presents the still ongoing, uncontrolled, prospective basket study LIBRETTO-001.

The study started in 2017 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, subjects 12 years and older with locally advanced or metastatic solid tumours with RET alteration were enrolled into different cohorts.

For the present therapeutic indication, adults and adolescents 12 years and older with advanced RET-mutant MTC without prior systemic therapy are relevant. The sub-population submitted by the pharmaceutical company comprises 142 patients. Of these, 27 patients (19.0%) were already receiving systemic prior therapy, which was a multikinase inhibitor in 10 patients. According to the pharmaceutical company, this did not include prior therapy with cabozantinib or vandetanib.

The data presented include patients from both phase 1 and phase 2 of the study. Part of the submitted sub-population was treated differently from the product information. This involved a different starting dose (19 patients, 13.4%), a dose reduction to 60 mg (15 patients) and treatment beyond disease progression (15 patients).

According to the pharmaceutical company, 5 data cut-offs are available from the LIBRETTO-001 study: Data cut-off 1 of 17.06.2019 (interim analysis), data cut-off 2 of 16.12.2019 (interim analysis), data cut-off 3 of 30.03.2020 (requested or conformity data cut-off for regulatory authorities), data cut-off 4 of 15.06.2021 (interim analysis), data cut-off 5 of 24.09.2021 (in agreement with regulatory authority; limited to part of the cohorts)

Comparator data

The pharmaceutical company presents the results of the uncontrolled LIBRETTO-001 study and performs descriptive observations of the results. The results from the LIBRETTO-001 study alone are unsuitable for assessing the additional benefit of selpercatinib as they do not allow a comparison with the appropriate comparator therapy. For the comparison with the appropriate comparator therapy, the pharmaceutical company compares the results of the 4th data cut-off (15.06.2021) for the endpoints of overall survival, PFS, tumour response and for the side effects endpoint category for its sub-population with the results of the 5 studies of its study pool on the comparison side: EXAM study, Koehler 2022 study, 104 study, 008 study and Valerio 2020 study

The pharmaceutical company presents separate indirect comparisons of the LIBRETTO-001 study with the individual arms from the various studies on the comparison side in the form of both unweighted comparisons and matching-adjusted-indirect-comparison (MAIC) analyses.

For the endpoints of overall survival, PFS and individual tumour response categories, Kaplan-Meier curves were available from the respective sources, from which data generated were used for time-to-event analyses. For further categories of tumour response and for the side effects endpoint category, the pharmaceutical company calculates approximate relative risks with 95% confidence intervals.

EXAM

The EXAM study is a double-blind, international, multicentre RCT comparing cabozantinib with placebo. A total of 330 patients ≥ 18 years with unresectable, locally advanced or metastatic MTC were enrolled in the study. The pharmaceutical company considers the sub-population of 107 patients with confirmed positive RET mutational status who were treated with cabozantinib for the comparisons on PFS and endpoints in the side effects category.

Koehler 2022

In the Koehler 2022 study, registry data of adult patients diagnosed with locally advanced or metastatic MTC were retrospectively analysed. For its comparisons of overall survival, PFS, tumour response and endpoints in the side effects category, the pharmaceutical company uses the sub-population of 36 patients with positive RET mutational status who were treated with vandetanib or cabozantinib in the first-line therapy.

104 study

The 104 study is a non-interventional observational study of vandetanib-treated adult patients with symptomatic, aggressive, locally advanced or metastatic MTC. The pharmaceutical company takes into account results on 55 patients with RET-positive tumours for its comparisons on PFS, tumour response and endpoints in the side effects category.

008 study

The 008 study is a non-controlled, multicentre phase 2 study on vandetanib treatment. For comparisons on tumour response and side effects, the pharmaceutical company uses 30 enrolled adult patients with locally advanced or metastatic hereditary MTC and evidence of a RET germline mutation.

Valerio 2020

The Valerio 2020 study is a single-arm observational study that enrols patients who have been treated with vandetanib in various clinical studies as well as after marketing authorisation at a study site in Italy. The study enrolled 79 adult patients with locally advanced or metastatic MTC, which the pharmaceutical company uses for comparisons of PFS and side effects.

Comparisons of individual arms from different studies

The comparisons of individual arms from different studies submitted by the pharmaceutical company are unsuitable for deriving statements on the additional benefit, as the studies on the intervention and comparison side are not comparable with regard to the patients enrolled.

With regard to the course of the disease, there are differences in the time interval between the diagnosis of the disease and the start of therapy with selpercatinib or the comparator therapy. In the LIBRETTO-001 study, the time between initial diagnosis and start of therapy was either longer (vs Koehler 2022 study or Valerio 2020 study), shorter (vs study 008) or there was no information on the time between initial diagnosis and start of treatment (study 104).

There are also potential differences between patient populations when it comes to the stage of the disease. For the sub-population of the LIBRETTO-001 study used by the pharmaceutical company, it remains unclear how many of the patients were in stage IVC. In contrast, the vast majority of patients in the studies on the comparison side are assigned to stage IVC.

The assumption of differences in the study populations is additionally supported by the different approved therapeutic indications for selpercatinib and vandetanib. According to the product information, in contrast to selpercatinib, the use of vandetanib is limited to the treatment of aggressive and symptomatic MTC, so that in comparison to the LIBRETTO-001 study, patients with a more advanced stage of the disease and/or a more aggressive course of the disease could have been enrolled in the studies on the comparator side.

Further differences between the patient population of the LIBRETTO-001 study and the comparator study arise with regard to the healthcare context (vs Koehler 2022 study), the inclusion criterion of radiographic evidence of tumour progression (vs Koehler 2022 study, 104 study and 008 study), the tumour burden (vs EXAM study) and the percentage of patients with hereditary MTC and RET germline mutation (vs 008 study). In addition, in the studies considered by the pharmaceutical company, with the exception of the Koehler 202 study, a part of the population was no longer in first-line therapy or no information on prior therapies was available (EXAM study or 104 study).

In summary, the comparisons of individual arms from different studies submitted by the pharmaceutical company are unsuitable for the assessment of the additional benefit, as the patient populations in the studies on the intervention and comparison side are not comparable with regard to the course of the disease and/or the aggressiveness of the disease.

Overall assessment

The results of the single-arm LIBRETTO-001 study presented alone are unsuitable for assessing the additional benefit of selpercatinib as they do not allow a comparison with the appropriate comparator therapy.

The pharmaceutical company presents separate indirect comparisons of the LIBRETTO-001 study with the individual arms from the various studies on the comparison side in the form of both unweighted comparisons and matching-adjusted-indirect-comparison (MAIC) analyses.

The presented indirect comparison with individual arms from different studies in the form of a non-weighted comparison is unsuitable for deriving statements on the additional benefit, as the studies on the intervention and comparison side are not comparable with regard to the patients enrolled.

Overall, the data presented are unsuitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of selpercatinib as monotherapy in adults and adolescents 12 years and above with advanced RET-mutant medullary thyroid cancer (MTC) is not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of selpercatinib finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The pharmaceutical company is obliged to submit further clinical data on the safety and efficacy of selpercatinib to the EMA for review.

Regarding the evidence to be provided, the EMA requires that the results of the phase III LIBRETTO-531 study be submitted to confirm the efficacy and safety of selpercatinib in the treatment of adults and adolescents 12 years and above with advanced RET-mutant medullary thyroid cancer (MTC) compared to the treatment with cabozantinib or vandetanib. The study report is expected on 28 February 2025.

The patient population of the LIBRETTO-531 study includes patients with an MTC in the first-line therapy. Thus, further clinical data are expected, which may be relevant for the assessment of the benefit of the medicinal product in the first-line therapy. Against this background, it is justified to limit in time the resolution until further scientific evidence is available for the assessment of the additional benefit of selpercatinib. The limitation enables the expected results from the LIBRETTO-531 study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V.

For this purpose, the G-BA considers a limitation of the resolution until 1 June 2025 to be appropriate.

Conditions of the limitation:

For the new benefit assessment after expiry of the deadline, the LIBRETTO-531 study results on overall survival and on all other patient-relevant endpoints used for the evidence of an additional benefit are to be presented in the dossier.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, No. 7 VerfO, the procedure for the benefit assessment of the medicinal product selpercatinib recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of selpercatinib in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product selpercatinib can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1, paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Retsevmo with the active ingredient selpercatinib.

This medicinal product was approved under “special conditions” 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 above with advanced medullary RET receptor tyrosine kinase (rearranged during transfection - RET)-mutant thyroid cancer in first-line therapy.

Vandetanib or cabozantinib is determined as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company submitted the results from the ongoing, prospective LIBRETTO-001 basket study for the treatment with selpercatinib. This is an uncontrolled study and therefore, does not include a comparator group.

The pharmaceutical company presents separate indirect comparisons of the LIBRETTO-001 study with the individual arms from the various studies on the comparison side in the form of both unweighted comparisons and matching-adjusted-indirect-comparison (MAIC) analyses.

The presented indirect comparison with individual arms from different studies in the form of a non-weighted comparison is unsuitable for deriving statements on the additional benefit, as the studies on the intervention and comparison side are not comparable with regard to the patients enrolled.

Overall, the indirect comparisons presented are unsuitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of selpercatinib as monotherapy in adults and adolescents 12 years and above with advanced medullary RET receptor tyrosine kinase (rearranged during transfection - RET)-mutant thyroid cancer in first-line therapy is not proven.

The resolution is valid until 1 June 2025, as further clinical data are expected from the phase 3 LIBRETTO-531 study, which investigates selpercatinib in comparison with cabozantinib or vandetanib.

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).

In the derivation, the G-BA only considers patients in the first-line therapy. The resolution shall be based on the information from the dossier and the adjustments submitted by the pharmaceutical company in the context of the written statement.

Uncertainties exist regarding the size of the target population. This includes the non-consideration of patients, diagnosed with early stage medullary thyroid cancer and eligible for the target population only during the course of the disease due to disease progression. However, the number of these patients with disease progression is estimated to be low since the relative survival of patients diagnosed at an early stage is very high, even after several years.

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: 8 December 2022):

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 experienced in the treatment of adults with thyroid cancer, and specialists in internal medicine, endocrinology and diabetology, as well as other specialists participating in the Oncology Agreement.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

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: 1 March 2023).

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, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied (average body weight for 12-year-olds 47.1 kg, 16-year-olds 65.2 kg and for adults 77.0 kg, average height for 12-year-olds 1.56 m, for 16-year-olds 1.73 m and for adults 1.72 m).[2] From this, a body surface area of 1.44 m^2 is calculated for 12-year-olds, 1.78 m^2 for 16-year-olds and 1.90 m^2 for adults (calculation according to Du Bois 1916).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

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

2 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Treatment period:

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	365	1	365
Appropriate comparator therapy				
Cabozantinib	Continuously, 1 x daily	365	1	365
Vandetanib BSA 1.2 to < 1.6	First year of treatment: 8-week starting dose 1x daily according to 7-day schedule: 100 mg - 200 mg 100 mg - 200 mg 100 mg - 200 mg 100 mg From week 9: 1 x 200 mg daily	First year of treatment: 8-week starting dose: 1 x daily From week 9: 1 x daily	1	365
	Subsequent year: 1 x 200 mg daily	Subsequent year: 1 x daily	1	365
Vandetanib BSA > 1.6	First year of treatment: 8-week starting dose 1 x 200 mg daily From week 9: 1 x 300 mg daily	First year of treatment: 8-week starting dose: 1 x daily From week 9: 1 x daily	1	365
	Subsequent year: 1 x 300 mg daily	Subsequent year: 1 x daily	1	365
Vandetanib (Adults)	Continuously, 1 x 300 mg daily	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Selpercatinib	120 mg – 160 mg	240 mg – 320 mg	2 x 40 mg + 2 x 80 mg – 4 x 80 mg	365	730 x 40 mg + 730 x 80 mg – 1,460 x 80 mg
Appropriate comparator therapy					
Cabozantinib[3]	140 mg	140 mg	1 x 80 mg + 3 x 20 mg	365	365 x 80 mg + 1,095 x 20 mg
Vandetanib BSA 1.2 to < 1.6	100/200 mg	<u>First treatment year:</u> 8-week starting dose According to a 7-day schedule: 100 mg - 200 mg 100 mg - 200 mg 100 mg - 200 mg 100 mg	<u>First treatment year:</u> 8-week starting dose: 1 x 100 mg/ 2 x 100 mg	56	80 x 100 mg
		From week 9: 200 mg	From week 9: 2 x 100 mg	309	618 x 100 mg
		<u>Subsequent year:</u> 200 mg	<u>Subsequent year:</u> 2 x 100 mg	365	730 x 100 mg
Vandetanib BSA > 1.6	200/300 mg	<u>First treatment year:</u>	<u>First treatment year:</u>		

[3] 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 day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
		8-week starting dose: 200 mg	8-week starting dose: 2 x 100 mg	56	112 x 100 mg
		From week 9: 300 mg	From week 9: 1 x 300 mg	309	309 x 300 mg
		Subsequent year: 300 mg	Subsequent year: 1 x 300 mg	365	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	€ 3,104.38	€ 2.00	€ 298.29	€ 2,804.09
Selpercatinib 80 mg	112 HC	€ 4,119.95	€ 2.00	€ 397.72	€ 3,720.23
Appropriate comparator therapy					
Cabozantinib 20/80 mg (for 28 days)	112 HC	€ 5,502.32	€ 2.00	€ 533.05	€ 4,967.27
Vandetanib 100 mg	30 FCT	€ 2,408.27	€ 2.00	€ 230.14	€ 2,176.13
Vandetanib 300 mg	30 FCT	€ 4,758.93	€ 2.00	€ 460.27	€ 4,296.66
Abbreviations: FCT = film-coated tablets; HC = hard capsules					

LAUER-TAXE® last revised: 1 March 2023

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 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 Selpercatinib

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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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.

On 30 September 2022, 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 2 VerfO.

By letter dated 4 October 2022 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 22 December 2022, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2023. The deadline for submitting written statements was 23 January 2023.

The oral hearing was held on 6 February 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 March 2023, and the proposed resolution was approved.

At its session on 16 March 2023, 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
Working group Section 35a	31 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 February 2023	Conduct of the oral hearing
Working group Section 35a	14 February 2023 28 February 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure

Subcommittee Medicinal products	7 March 2023	Concluding discussion of the draft resolution
Plenum	16 March 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 March 2023

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

Prof. Hecken