Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V

Selpercatinib (thyroid cancer, RET mutated, after prior therapy with cabozantinib and/or vandetanib, ≥ 12 years)

of 2 September 2021

Contents

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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 studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
6. Requirements for a quality-assured application.

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

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

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient selpercatinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 March 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 12 March 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de), on 15 June 2021, thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of selpercatinib compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements

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submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of 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-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib .

Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.

Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

Therapeutic indication of the resolution (resolution from the 2 September 2021):

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults and adolescents 12 years and older with advanced RET receptor tyrosine kinase (rearranged during transfection - RET) mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

Patient-individual therapy under the selection of

- cabozantinib,
- vandetanib and
- best supportive care

considering the previous therapy and the general condition.

1 General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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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 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 Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. The comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally accepted state of medical knowledge.

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

on 1. According to the authorisation status, the two protein kinase inhibitors cabozantinib and vandetanib are available for advanced medullary thyroid cancer.

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 22.01.2015
- Vandetanib: resolutions of 05.09.2013 and 06.07.2017

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication.

At present, no specific treatment recommendations depend on the presence of a RET mutation. Furthermore, the available evidence does not suggest that patients with advanced medullary thyroid cancer and a RET mutation would be treated differently than with current standard therapies.

No national guidelines for the treatment of patients with an MTC have been identified. The systematic reviews and international guidelines considered predominantly recommend therapy with the tyrosine kinase inhibitors (TKIs) cabozantinib or vandetanib as systemic therapy for patients with MTC with symptomatic or progressive disease.

In the present benefit assessment statements, clinical experts stated that in the reality of care, after treatment with one of the two TKIs cabozantinib or vandetanib, a switch to the other active ingredient is carried out in the subsequent line if the appropriate conditions are met.

The therapeutic indication also includes patients for whom systemic therapy is indicated but who are not eligible for therapy with cabozantinib or vandetanib or for a

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change to the other active ingredient, e.g. because of their disease characteristics. Furthermore, patients are included for whom antineoplastic therapy options are usually no longer available after previous therapy. According to the current state of medical knowledge, there is no specific standard therapy for these patients. Therefore, the best supportive care was determined as an appropriate comparator therapy for these patients in the context of patient-individual therapy.

Change of the appropriate comparator therapy:

Originally, the appropriate comparator therapy was determined as follows:

Adults and adolescents 12 years and older with advanced RET receptor tyrosine kinase (rearranged during transfection - RET) mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

Best supportive care

Within the framework of the written statement procedure, the clinical experts explained that patients are treated with both TKIs cabozantinib and vandetanib alternately in the provision of care if the appropriate conditions are met. In case of intolerance or progression of the disease, patients receive the other TKI in the subsequent line, depending on their general condition and side effects after treatment with one TKI.

In view of the statements of the clinical experts, it is now considered appropriate by the G-BA for the present assessment to consider this therapy option in the context of a patient-individual therapy with the selection of cabozantinib, vandetanib and best supportive care, taking into account the previous therapy and the general condition.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

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

2.1.3 Extent and probability of the additional benefit

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

For the treatment of adults and adolescents 12 years and older with advanced RET receptor tyrosine kinase (rearranged during transfection - RET) mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib, an additional benefit is not proven

Justification:

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

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

In the first phase, the study investigated dose escalation in patients 12 years of age and older with locally advanced or metastatic solid tumours regardless of RET-status and prior treatment who had progression on or were intolerant to prior standard therapies. In the second phase, subjects 12 years of age and older with locally advanced or metastatic solid tumours with a RET-alteration were enrolled in different cohorts. Cohort 3, relevant for the present benefit assessment, included patients with advanced medullary thyroid cancer with RET mutation and progression on standard therapy or intolerance to standard therapy.

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The pharmaceutical company uses the sub-population of adults with RET-mutated advanced MTC who have previously received treatment with cabozantinib and/or vandetanib for comparisons.

The results from the LIBRETTO-001 study alone are not suitable for assessing the additional benefit of selpercatinib, as they do not allow a comparison with the appropriate comparator therapy. For comparison with the appropriate comparator therapy, the pharmaceutical company identifies the double-blind, international, multi-centre study EXAM comparing cabozantinib with placebo and the double-blind, international, multi-centre study Wells 2012 comparing vandetanib with placebo.

Comparisons with the Wells 2012 study are not possible due to a lack of data on the appropriate sub-population.

The pharmaceutical company submits a non-adjusted indirect comparison. The presented comparisons of individual arms from the EXAM study are not suitable for statements on the additional benefit, as not all inclusion criteria of the research question are fulfilled in the study. Furthermore, the bias in magnitude and direction resulting from comparing individual arms from different studies cannot be assessed even by the sensitivity analyses presented. Furthermore, the observed effects are not so large that they cannot be explained by bias alone.

Therefore, no adequate data are available to assess the additional benefit of selpercatinib compared to the appropriate comparator therapy. Therefore, an additional benefit is not proven.

Selpercatinib may represent a relevant therapeutic option in the present therapeutic indication.

2.1.4 Summary of the assessment

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

Retsevmo was approved under special conditions.

Selpercatinib as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

As appropriate comparator therapy, the G-BA determined a patient-individual therapy selecting cabozantinib, vandetanib and best supportive care; taking into account previous therapy and general condition.

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

The results from the LIBRETTO-001 study alone are not suitable for assessing the additional benefit of selpercatinib, as they do not allow a comparison with the appropriate comparator therapy.

The pharmaceutical company submits a non-adjusted indirect comparison. The comparisons of individual arms from the EXAM study are not suitable for statements on additional benefit, as not all inclusion criteria of the research question are fulfilled in the study. Furthermore, the bias in magnitude and direction resulting from comparing individual arms from different studies cannot be assessed even by the sensitivity analyses presented. Furthermore, the observed effects are not so broad that they cannot be explained by bias alone.

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No adequate data are available to assess the additional benefit of selpercatinib compared to the appropriate comparator therapy. Therefore, an additional benefit is not proven.

Selpercatinib may represent a relevant therapeutic option in the present therapeutic indication.

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

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

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier. The data on the number of people with the disease is underestimated. This is mainly due to the underestimation of the proportion of patients suitable for first-line systemic therapy.

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: 29 July 2021):

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

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

This medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency (EMA) will assess new information on this medicinal product at least annually and update the product information for healthcare professionals as necessary.

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

2.4 Treatment costs

The treatment costs are based on the product information as well as the information in the LAUER-TAXE® (last revised: 15 August 2021).

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.

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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 of 12-year-olds 47.1 kg and of adults 77.0 kg, average height of 12-year-olds 1.56 m and for adults: 1.72 m).[2] This results in a body surface area of 1.44 m^2 for 12-year-olds and 1.90 m^2 for adults (calculated according to Du Bois 1916)

For the cost representation, only the doses 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.

In the present therapeutic indication, cabozantinib is approved only for adults.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Selpercatinib	continuously, 2 x day	365	1	365
Best supportive care	Patient-individual			
Appropriate comparator therapy				
Best supportive care	Patient-individual			
Cabozantinib	continuously, 1 x day	365	1	365
Vandetanib	continuously, 1 x day	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Selpercatinib	120 mg – 160 mg	240 mg – 320 mg	6 x 40 mg – 4 x 80 mg	365	2,190 x 40 mg – 1,460 x 80 mg
Best supportive care	Patient-individual				

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

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Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Best supportive care	Patient-individual				
Cabozantinib (≥ 18 years)	140 mg	140 mg	1 x 80 mg + 3 x 20 mg	365	365 x 80 mg + 1,095 x 20 mg
Vandetanib	100 mg – 300 mg	100 mg – 300 mg			

Costs:

To improve comparability, the costs of the medicinal products were approximated both based on the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on 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	60 HC	€ 3,719.15	€ 1.77	€ 209.13	€ 3,508.25
Selpercatinib 80 mg	60 HC	€ 7,380.94	€ 1.77	€ 418.25	€ 6,960.92
Best supportive care	Patient-individual				
Appropriate comparator therapy					
Best supportive care	Patient-individual				
Cabozantinib 20/80 mg (for 28 days)	112 HC	€ 5,695.60	€ 1.77	€ 322.00	€ 5,371.83
Vandetanib 100 mg	30 FCT	€ 2,408.04	€ 1.77	€ 134.25	€ 2,272.02
Vandetanib 300 mg	30 FCT	€ 4,758.69	€ 1.77	€ 268.49	€ 4,488.43
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 considered as costs for additionally required SHI services.

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

Because there are no regular differences in the necessary 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.

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 10 March 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 9 February 2021.

On 12 March 2021, 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 1, sentence 2 VerfO.

By letter dated 15 March 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient selpercatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 June 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 June 2021. The deadline for submitting written statements was 6 July 2021.

The oral hearing was held on 26 July 2021.

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 the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 24 August 2021, and the proposed resolution was approved.

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At its session on 2 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	18.08.2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	18.08.2021	New implementation of the appropriate comparator therapy
Working group Section 35a	18.08.2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	18.08.2021	Conduct of the oral hearing
Working group Section 35a	18.08.2021 18.08.2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	18.08.2021	Concluding consultation of the draft resolution
Plenum	18.08.2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 September 2021

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

Prof. Hecken

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