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
Cabozantinib (new therapeutic indication:
thyroid carcinoma, refractory to radioactive iodine, after prior systemic therapy)

of 1 December 2022

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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient cabozantinib (Cabometyx) was listed for the first time on 1 November 2016 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 29 April 2022, Cabometyx 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 24 May 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 cabozantinib 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) (*Cabometyx is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy*).

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 1 September 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of cabozantinib 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, the statements submitted in the written statement and oral hearing procedure, and the addendum 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 cabozantinib.

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 Cabozantinib (Cabometyx) in accordance with the product information

Cabometyx is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

Therapeutic indication of the resolution (resolution of 01.12.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy

Appropriate comparator therapy:

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

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:

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. According to the authorisation status, the protein kinase inhibitors sorafenib, lenvatinib and selpercatinib as well as the cytostatic agent doxorubicin are available for locally advanced or metastatic differentiated thyroid carcinoma.

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

On 3. Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the therapeutic indication of locally advanced or metastatic differentiated thyroid carcinoma in adults:

- Lenvatinib: Resolution of 15.08.2019
- Selpercatinib: Resolution of 02.09.2021

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 (see “Information on Appropriate 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.

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.

According to the available evidence and the written statements of the scientific-medical societies on the question of comparator therapy, the tyrosine kinase inhibitors (TKIs) sorafenib or lenvatinib are recommended as therapy for patients with advanced differentiated thyroid carcinoma with disease progression and/or symptomatic disease. With regard to the present treatment setting - progression during or after a previous systemic therapy - there is very little evidence regarding subsequent therapies.

In the statements of the scientific-medical societies on the benefit assessment of selpercatinib (resolution of 02.09.2021) in a similar therapeutic indication, 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.

This was confirmed in the written statement of the scientific-medical societies on the question of comparator therapy in the present therapeutic indication.

For the TKI lenvatinib, there is a resolution of 15.08.2019 on the benefit assessment according to Section 35a SGB V, according to which an additional benefit of sorafenib compared to the appropriate comparator therapy is not proven. No suitable data were available in the benefit assessment.

In the benefit assessment of selpercatinib in advanced thyroid carcinoma with existing fusion of the RET receptor tyrosine kinase (rearranged during transfection - RET), the resolution of 02.09.2021, it was determined 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 not identified to be an appropriate comparator therapy for this resolution.

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 according to the present therapeutic indication does not correspond to the generally accepted state of medical knowledge.

In the overall assessment, 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.

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 cabozantinib is assessed as follows:

Adults with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy

An additional benefit is not proven.

Justification:

For the treatment of adults with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy, the pharmaceutical company does not submit data for the assessment of additional benefit. Therefore, an additional benefit 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 cabozantinib. The therapeutic indication assessed here is as follows:

"Cabozantinib is indicated as monotherapy for the treatment of adults with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy."

The G-BA determined that the appropriate comparator therapy was 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 not proven.

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

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

The resolution is based on the data from the written statement of the pharmaceutical company, since in the overall analysis the new derivation better reflects the number of patients than the patient numbers shown in the dossier.

However, the lower limit is still an underestimate. This is particularly due to the underestimation of patients with first-line systemic therapy. The upper limit range seems more appropriate to reflect the number of patients in the SHI target population.

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 Cabometyx (active ingredient: cabozantinib) at the following publicly accessible link (last access: 10 November 2022):

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

Treatment with cabozantinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology as well as specialists in internal medicine, endocrinology and diabetology, and other specialists participating in the Oncology Agreement experienced in the treatment of patients with thyroid carcinoma

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 November 2022).

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.

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.

Best supportive care:

The treatment costs for best supportive care are different for each individual patient. Because best supportive care has been determined as the appropriate comparator therapy as part of a patient-individual therapy, best supportive care 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:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Cabozantinib	continuously, 1 x daily	365	1	365
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			
Lenvatinib	continuously, 1 x daily	365	1	365
Sorafenib	continuously, 2 x daily	365	1	365

Consumption:

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					
Cabozantinib	60 mg	60 mg	1 x 60 mg	365	365 x 60 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Lenvatinib	24 mg	24 mg	2 x 10 mg + 1 x 4 mg	365	730 x 10 mg + 365 x 4 mg
Sorafenib	400 mg	800 mg	4 x 200 mg	365	1460 x 200 mg

Costs:

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					
Cabozantinib 60 mg	30 FCT	€ 5,516.60	€ 1.77	€ 311.76	€ 5,203.07
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Lenvatinib 10 mg	30 HC	€ 1,853.45	€ 1.77	€ 102.56	€ 1,749.12
Lenvatinib 4 mg	30 HC	€ 1,626.52	€ 1.77	€ 89.60	€ 1,535.15
Sorafenib 200 mg	112 FCT	€ 373.11[2]	€ 1.77	€ 17.17	€ 354.17
Abbreviations: FCT = film-coated tablet, HC = hard capsule					

LAUER-TAXE® last revised: 15 November 2022

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 pursuant to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Cabozantinib

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination

[2] The costs are represented on the basis of the low-priced medicinal products, also taking into account the requirements of Section 129 SGB V and the possibility of prescribing medicinal products under their active ingredient name. Irrespective of this, the prescription of corresponding medicinal products must take into account the respective approved therapeutic indications.

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 09 November 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 24 May 2022, the pharmaceutical company submitted a dossier for the benefit assessment of cabozantinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 27 May 2022 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 cabozantinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 18 August 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 September 2022. The deadline for submitting written statements was 22 September 2022.

The oral hearing was held on 10 October 2022.

By letter dated 11 October 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 10 November 2022.

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 22 November 2022, and the proposed resolution was approved.

At its session on 1 December 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 November 2021	Determination of the appropriate comparator therapy
Working group Section 35a	4 October 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 October 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 October 2022 15 November 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	22 November 2022	Concluding discussion of the draft resolution
Plenum	1 December 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 01 December 2022

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

Prof. Hecken