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 (reassessment after the deadline: thyroid carcinoma.)

of 16 December 2021

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.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified, indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the marketing authorisation studies by the G-BA, indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA 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 pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient cabozantinib (Cometriq) to be assessed for the first time on 1 August 2014. For the resolution of 22 January 2015 made by the G-BA in this procedure, a time limit of 1 July 2021 was pronounced.

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

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 30 June 2021.

Cabozantinib indicated for the treatment of adult patients with progressive, unresectable, locally advanced or metastatic medullary thyroid carcinoma is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 October 2021 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G21-20) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of cabozantinib.

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

1.1 Additional benefit of the medicinal product

1.1.1 Approved therapeutic indication of Cabozantinib (Cometriq) in accordance with the product information

Cometriq is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

Therapeutic indication of the resolution (resolution of 16 December 2021):

see approved therapeutic indication

1.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of cabozantinib for the treatment of adult patients with progressive, unresectable, locally advanced or metastatic medullary thyroid carcinoma is assessed as follows:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

EXAM study

The pharmaceutical company submits the results of the EXAM marketing authorisation study (final data cut-off of 28 August 2014) for the new benefit assessment of cabozantinib in the present therapeutic indication. This study is a randomised double-blind, international, multicentre phase III study. The study was conducted in 114 sites across 23 countries worldwide from June 2008 to September 2020.

The study enrolled adults with unresectable, locally advanced or metastatic medullary thyroid carcinoma and randomised in a 2:1 ratio to an intervention group in which cabozantinib was given or to a control group in which placebo was given. The intention-to-treat (ITT) population comprises 219 patients in the intervention group and 111 patients in the control group.

The primary endpoint was "progression-free survival" (PFS). In addition, data were presented on the secondary endpoints of overall survival, morbidity, and quality of life using the MDASI-Thy questionnaire (MD Anderson Symptom Inventory - Thyroid Cancer Module) and side effects.

EXAMINER study

The pharmaceutical company also presents data from the EXAMINER study in the dossier with a data cut-off of 15 July 2020. This is an ongoing multicentre, randomised, controlled, double-blind phase IV study.

This study examines the efficacy, safety, and tolerability of cabozantinib at a daily dose of 60 mg compared to 140 mg in adults with progressive, metastatic medullary thyroid cancer using a non-inferiority study design. Patients were randomised to the two treatment arms in a 1:1 ratio. Stratified randomisation was performed by RET-M918 mutational status (positive, negative, unknown). An unknown RET-M918 mutational status was possible in up to 10% of participants.

In the cabozantinib 60 mg arm, treatment was started at a dose of 60 mg per day. As a rule, this is not recommended in the product information. Subsequently, there were two dose reductions to 40 mg and 20 mg. The mean daily dose in this study arm was 39 mg. A reduction to less than 60 mg is not in compliance with the marketing authorisation. For this reason, the EXAMINER study is not used for the present assessment. An adjusted indirect comparison is not available.

Mortality

In the EXAM study, the endpoint of "overall survival" was assessed as a secondary endpoint. In the total population, no statistically significant difference was detected between the treatment groups for the endpoint of overall survival.

Relevant subgroup effects were observed regarding the RET-M918T mutational status of the patients. Statistically significant differences in overall survival to the advantage of cabozantinib were seen in the subgroup with positive RET-M918T mutational status. In contrast, in the subgroup of patients with negative RET-M918T mutational status and with unknown RET-M918T mutational status, no statistically significant differences in overall survival were observed between the intervention and control arms.

The significance and interpretability of the results of the subgroup analysis are limited by a number of factors. Subgroup analysis to investigate the presence of the specific RET-M918T mutation was not predefined in the study protocol. In addition, the reliability of the determination of the RET mutational status in the EXAM study should be questioned.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the EXAM study. PFS was defined as the time from randomisation to disease progression or death. Disease progression was assessed using the modified Response Evaluation Criteria in Solid Tumours (mRECIST) by a blinded, independent committee to assess the radiographic findings.

There was a statistically significant difference between the treatment arms to the advantage of cabozantinib versus placebo.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an

independent endpoint via the endpoint "overall survival". The morbidity component of "disease progression" is assessed according to mRECIST criteria and thus, not symptom-related, but by means of imaging procedures.

Symptomatology and also tumour-related symptoms were assessed separately in the study using the MDASI-Thy questionnaire. In addition, health-related quality of life was assessed using the quality of life scales of the MDASI-Thy questionnaire.

From the available data, it remains unclear whether the statistically significant prolonged time of progression-free survival – radiologically determined disease progression according to RECIST criteria – is associated with an improvement in symptomatology or health-related quality of life.

The results of the PFS endpoint are therefore not used to reliably state the extent of additional benefit.

Symptomatology

In the EXAM study, data on symptomatology were collected using the symptom scales of the MDASI-Thy questionnaire. The required return rates were only achieved at baseline, which is why no assessable data are available.

With regard to morbidity, an additional benefit is therefore not proven.

Health-related quality of life

In the EXAM study, quality of life was assessed using the quality of life scales of the MDASI-Thy questionnaire. The required return rates were only achieved at baseline, which is why no assessable data are available.

With regard to health-related quality of life, an additional benefit is therefore not proven.

Side effects

Adverse events (AEs) in total

Adverse events occurred in almost all study participants.

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

There was a statistically significant difference in serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs to the disadvantage of cabozantinib.

AEs of special interest

For the serious AEs "Gastrointestinal disorders" and "Metabolism and nutrition disorders", there is a statistically significant difference to the disadvantage of cabozantinib.

There was a statistically significant difference in severe adverse events with CTCAE grade ≥ 3 to the disadvantage of cabozantinib for "Gastrointestinal disorders", "General disorders and administration site conditions", "Metabolism and nutrition disorders", "Nervous system disorders" and "Vascular disorders".

The overall assessment of the results on side effects shows clear differences to the disadvantage of cabozantinib, in particular with regard to severe and serious adverse events.

Overall assessment

For the assessment of the additional benefit of cabozantinib in the treatment of adults with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer, results for the endpoints of overall survival and side effects are available from the randomised, double-blind phase III EXAM study.

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups considering the total population. There is a statistically significant difference to the advantage of cabozantinib in the subgroup of patients with positive RET-M918T mutational status, whereas there is no statistically significant difference in the subgroup of patients with negative RET-M918T mutational status and in the subgroup of patients with unknown RET-M918T mutational status. The significance and interpretability of the results of the subgroup analysis are limited by a number of factors.

No assessable data are available for the endpoint categories of morbidity and health-related quality of life.

Overall, in terms of side effects, there are clear differences to the disadvantage of cabozantinib, particularly in the severe and serious adverse events.

In the overall assessment of the present results, a statistically significant advantage with regard to overall survival in a subgroup contrasts with statistically significant disadvantages with regard to side effects for the total population. In the initial assessment of cabozantinib in the present therapeutic indication, a minor additional benefit was also identified pending further findings from data to be submitted after the deadline. However, the data submitted for a new benefit assessment after the deadline did not provide any new results relevant for the benefit assessment.

In the overall assessment, the G-BA classified the extent of the additional benefit of cabozantinib in the treatment of adults with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer as non-quantifiable because the scientific data basis does not allow quantification.

Significance of the evidence

The present EXAM study is a randomised, double-blind study. The risk of bias at the study level is estimated to be low.

The risk of bias at the endpoint level is estimated to be low for the endpoint of overall survival and high for that of adverse events.

No usable data on the symptomatology and health-related quality of life are available from the participants of the EXAM study. In the present advanced, palliative treatment setting, data on symptomatology and health-related quality of life are given high priority.

Based on these limitations, a hint for the identified additional benefit is established.

1.1.3 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient cabozantinib after expiry of the limitation of the period of validity of the resolution of 22 January 2015.

Cometriq was approved as an orphan drug for the treatment of adults with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer. The RCT EXAM study, comparing cabozantinib with placebo, is available.

There is no statistically significant difference for the endpoint of overall survival considering the total population. There is a statistically significant difference to the advantage of cabozantinib in the subgroup with positive RET-M918T mutational status whereas there is no statistically significant difference for negative and unknown RET-M918T mutational status.

No assessable data are available for morbidity and health-related quality of life.

In terms of side effects, there are statistically significant differences to the disadvantage of cabozantinib, particularly in the severe and serious AEs.

In the overall assessment, a statistically significant advantage for overall survival in a single subgroup contrasts with an overall statistically significant disadvantage for relevant side effects for the total population. In the initial assessment of cabozantinib in the present therapeutic indication, a minor additional benefit was also identified pending further findings from data to be submitted after the deadline. However, the data submitted for a new benefit assessment did not provide any new results relevant for the benefit assessment.

In the overall assessment, the G-BA classifies the extent of the additional benefit of cabozantinib in the present therapeutic indication as non-quantifiable because the scientific data basis does not allow quantification.

The significance of the evidence is classified as a "hint", especially since no usable data on symptomatology and health-related quality of life are available.

2.1 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 bases its resolution on the information from the dossier of the pharmaceutical company.

Uncertainties exist regarding the size of the target population. These include the stage classifications used by the pharmaceutical company and the underlying mortality rate.

In addition, patients, diagnosed with medullary thyroid cancer at an earlier stage and eligible for the target population only during the course of the disease due to disease progression, are not included. 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.

2.2 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 Cometriq (active ingredient: cabozantinib) at the following publicly accessible link (last access: 6 October 2021):

https://www.ema.europa.eu/en/documents/product-information/cometriq-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 endocrinology, and specialists participating in the Oncology Agreement experienced in the treatment of patients with medullary thyroid carcinoma.

2.3 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 December 2021).

Treatment period:

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.

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	1 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	140 mg	140 mg	1 x 80 mg 3 x 20 mg	365	365 x 80 mg 1095 x 20 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 130 a 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:					
Cabozantinib	112 HC	€ 5,695.60	€ 1.77	€ 322.00	€ 5,371.83

LAUER-TAXE® last revised: 1 December 2021

HC: hard capsules

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.

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

On 30 June 2021, 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 5 VerfO.

The benefit assessment of the G-BA was published on 1 October 2021 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 October 2021.

The oral hearing was held on 8 November 2021.

An amendment to the benefit assessment with a supplementary assessment was submitted on 18 November 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 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 7 December 2021, and the draft resolution was approved.

At its session on 16 December 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	22 October 2013	Information of the benefit assessment of the G-BA
Working group Section 35a	3 November 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	8 November 2021	Conduct of the oral hearing, Authorisation of an amendment
Working group Section 35a	17 November 2021; 1 December 2021	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal product	7 December 2021	Concluding discussion of the draft resolution
Plenum	16 December 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 December 2021

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

Prof. Hecken