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

Vandetanib (reassessment after the deadline (medullary thyroid cancer))

of 18 March 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 is 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 vandetanib (Caprelsa) to be assessed for the first time on 8 March 2013. For the resolution of 5 September 2013 made by the G-BA in this procedure, a limitation up to 1 October 2021 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product vandetanib 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 September 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 3 January 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 vandetanib 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, 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 vandetanib.

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 Vandetanib (Caprelsa) according to product information

Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

Therapeutic indication of the resolution (resolution of 18 March 2022):

Adults with aggressive and symptomatic medullary thyroid cancer (MTC) and unresectable locally advanced or metastatic disease.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with aggressive and symptomatic medullary thyroid cancer (MTC) and unresectable locally advanced or metastatic disease

- Cabozantinib

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.

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

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. 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. Cabozantinib and vandetanib are approved medicinal products for the treatment of medullary thyroid cancer.

on 2. A non-medicinal treatment cannot be considered in the planned therapeutic indication.

on 3. Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V:
- Cabozantinib: resolutions of 22 January 2015 and 16 December 2021
- 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 systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to § 35a SGB V".

Systematic reviews, guidelines and the statements 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. The corresponding marketing authorisations of the two tyrosine kinase inhibitors mentioned also focus on these disease characteristics. Cabozantinib is therefore determined as the appropriate comparator therapy for the present new benefit assessment of vandetanib after expiry of the deadline.

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 vandetanib is assessed as follows:

An additional benefit is not proven for the treatment of adults with aggressive and symptomatic medullary thyroid cancer (MTC) and unresectable, locally advanced or metastatic disease.

Justification:

In order to comply with the deadline requirements of the G-BA, the pharmaceutical company submits the D4200C00104 study. The D4200C00104 study is a non-interventional, open-label, post-authorisation safety study that was requested by the European Medicines Agency from the pharmaceutical company to obtain further comprehensive clinical data on the safety and efficacy of vandetanib.

97 patients with aggressive and symptomatic, unresectable, locally advanced or metastatic medullary thyroid cancer with RET-positive or RET-negative mutation status were enrolled in the study. The patients were divided into two cohorts according to their mutational status. For the endpoints of mortality and side effects, results were presented separately for patients

with RET-positive or RET-negative status. The study commenced in February 2014 and was completed in December 2020.

The results from the D4200C00104 study alone are not suitable for assessing the additional benefit of vandetanib, as they do not allow a comparison with the appropriate comparator therapy.

Therefore, no data are available for the assessment of the additional benefit of vandetanib compared to the appropriate comparator therapy. An additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient vandetanib due to the expiry of the limitation of the resolution of 5 September 2013.

The assessment refers exclusively to the following patient population: Adults with aggressive and symptomatic medullary thyroid cancer (MTC) and unresectable locally advanced or metastatic disease.

In order to comply with the deadline requirements of the G-BA, the pharmaceutical company submits the D4200C00104 study. The D4200C00104 study is a non-interventional, open-label, post-authorisation safety study (PASS) that was requested by the European Medicines Agency (EMA) from the pharmaceutical company to obtain further comprehensive clinical data on the safety and efficacy of vandetanib.

The results from the D4200C00104 study alone are not suitable for assessing the additional benefit of vandetanib, as they do not allow a comparison with the appropriate comparator therapy.

Therefore, no data are available for the assessment of the additional benefit of vandetanib compared to the appropriate comparator therapy. 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 G-BA based its resolution on the patient numbers from the recently conducted benefit assessment of cabozantinib (resolution of 16 December 2021). Despite uncertainties, this number was seen in a largely plausible order of magnitude.

The number of patients in the target population submitted by the pharmaceutical company is subject to uncertainties overall. When comparing the number of patients in the target population of cabozantinib in a similar therapeutic indication, a lower number is expected in the target population of vandetanib. Therefore, the G-BA considers it appropriate to use the number of patients from the resolution on cabozantinib.

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 Caprelsa (active ingredient: vandetanib) at the following publicly accessible link (last access: 17 January 2022):

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

Treatment with vandetanib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and endocrinology, and other specialists participating in the Oncology Agreement, experienced in the therapy of patients with medullary thyroid cancer.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient pass. The training material for medical professionals includes, among others, instructions on how to manage the risks of QTc prolongations, Torsades de Pointes and posterior reversible encephalopathy syndrome associated with vandetanib.

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 2022).

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 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.

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				
Vandetanib	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Cabozantinib	Continuously, 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					
Vandetanib	300 mg	300 mg	1 x 300 mg	365	365 x 300 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
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 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					
Vandetanib 300 mg	30 FCT	€ 4,758.93	€ 1.77	€ 268.49	€ 4,488.67
Appropriate comparator therapy					
Cabozantinib 20 mg/80 mg 140 mg/day	112 HC	€ 5,695.84	€ 1.77	€ 322.00	€ 5,372.07
Abbreviations: FCT: = film-coated tablets; HC: hard capsules					

LAUER-TAXE® last revised: 1 March 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.

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 28 September 2011, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

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 26 October 2021.

On 30 September 2021, the pharmaceutical company submitted a dossier for the benefit assessment of vandetanib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 5 VerfO.

By letter dated 30 September 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 vandetanib.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 December 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 3 January 2022. The deadline for submitting written statements was 24 January 2022.

The oral hearing was held on 7 February 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 9 March 2022, and the proposed resolution was approved.

At its session on 18 March 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	28 September 2011	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	26 October 2021	New determination of the appropriate comparator therapy

Working group Section 35a	2 February 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	7 February 2022	Conduct of the oral hearing
Working group Section 35a	16 February 2022 2 March 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	9 March 2022	Concluding discussion of the draft resolution
Plenum	18 March 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 18 March 2022

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

Prof. Hecken