Justification

Gemeinsamer Bundesausschuss

to 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 Lenvatinib (evaluation after the withdrawal of orphan drug status)

of 15 August 2019

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 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 shall pass a resolution 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 medicinal product Lenvima® with the active ingredient lenvatinib was authorised for the first time as medicinal product for the treatment of a rare disease (orphan drug) under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999. This marketing authorisation as an orphan drug was granted for the following therapeutic indication:

“Lenvatinib (Lenvima®) is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)”.

For this therapeutic indication, the G-BA passed a resolution on 17 December 2015 on the benefit assessment of lenvatinib on the basis of the statutory regulations on the benefit assessment of drugs to treat orphan diseases (Section 35a, paragraph 1, sentence 11 SGB V).

On 1 August 2018, the orphan designation of Lenvima® was withdrawn from the community register of orphan drugs. Consequently, its status as an orphan drug expired. As a result, the pharmaceutical company was requested by the G-BA in a letter dated 8 November 2018 to submit evidence according to Chapter 5, Section 5, paragraphs 1 to 6 of the VerfO and to demonstrate the additional benefit compared with the appropriate comparator therapy.

On 14 February 2019, the pharmaceutical company submitted a dossier on the active ingredient Lenvatinib in due time (i.e. within three months of receipt of the request of the G-

BA) in corresponding application of Section 35a paragraph 1 sentence 11 SGB V in conjunction with Chapter 5, Section 8, paragraph 1, number 6 and Section 12, number 2 of the Rules of Procedure (VerfO) of the G-BA.

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 May 2019, 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 lenvatinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of lenvatinib.

In light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at 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 lenvatinib (Lenvima®) in accordance with product information

LENVIMA is indicated as monotherapy for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

2.1.2 Appropriate comparator therapy

Adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

- Sorafenib

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 according to 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 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. In addition to lenvatinib, the active ingredients sorafenib and doxorubicin are approved for this therapeutic indication.

On 2. Non-medicinal treatment is not considered.

On 3. A resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V has been passed on lenvatinib (resolution of 17 December 2015).

On 4. The generally accepted state of medical knowledge for the indication was established by means of a systematic search for guidelines and reviews of clinical studies.

Accordingly, the body of evidence is very limited in the present therapeutic indication. Relevant Cochrane and other systematic reviews could not be identified. International guidelines unanimously recommend treatment with tyrosine kinase inhibitors (TKI) in patients with progressive, radio-iodine refractory, locally advanced or metastatic DTC. The literature consistently identifies lenvatinib and sorafenib as the two active ingredients authorised for the indication under consideration. Other TKIs recommended in the guidelines are not authorised for the therapeutic indication. The guidelines under consideration reveal a low response rate to chemotherapy with doxorubicin in the absence of radioactive iodine storage, and it is not considered an equivalent treatment option.

In the overall view, sorafenib is therefore determined as an appropriate comparator therapy for the present benefit assessment of lenvatinib in the present therapeutic indication.

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 lenvatinib is assessed as follows:

For adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI), an additional benefit of lenvatinib as a monotherapy compared with sorafenib is not proven.

Justification:

In the absence of a direct comparative study of lenvatinib with the appropriate comparator therapy sorafenib, the pharmaceutical company presents an adjusted indirect comparison according to the method of Bucher *et al.* to prove an additional benefit. For this indirect comparison via the bridge comparator placebo, the pharmaceutical company includes the SELECT study with lenvatinib (vs placebo) and the DECISION study with sorafenib (vs placebo).

Both studies are randomised, double-blind, controlled, multi-centre Phase III studies.

SELECT

The study included 392 adult patients with histologically or cytologically confirmed diagnosis of a DTC (papillary, follicular, or Hürthle cell), who where assigned to either treatment with lenvatinib or a corresponding placebo at a ratio of 2:1. Randomisation was stratified by geographic region (Europe/North America/other), previous therapy targeted against vascular endothelial growth factors (VEGF) (0/1), and age (≤ 65/ > 65). Patients should have had a radiographically measurable disease and progression within 12 months prior to inclusion and have been 131 iodine-refractory or resistant.

Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. There were no restrictions regarding follow-up therapies. When disease progression occurred, patients were unblinded and switched to lenvatinib treatment if they belonged to the placebo arm. At the time of primary analysis, when 83% of patients had already switched from placebo arm to lenvatinib treatment, all patients were unblinded, and the remaining patients of the placebo arm were allowed to switch to lenvatinib.

The primary endpoint of the study was progression-free survival (PFS); other endpoints were overall survival and adverse events.

DECISION

The study included 417 adult patients with histologically or cytologically confirmed diagnosis of a DTC (papillary, follicular, Hürthle cell, or poorly differentiated), who where assigned to either treatment with sorafenib or a corresponding placebo at a ratio of 1:1. Randomisation was stratified by geographical region (Europe/North America/Asia) and age (≤ 60/> 60). Patients should have had a radiographically measurable disease and progression within 14 months prior to inclusion and have been 131 iodine-refractory.

Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. There were no restrictions regarding follow-up therapies. When disease progression occurred, patients could be unblinded and, at the physician's discretion, continue treatment with sorafenib or switch from the placebo arm to sorafenib treatment as long as a clinical benefit was observed.

After the primary analysis, at which time 71% of patients had already switched from the placebo arm to sorafenib, the remaining placebo arm patients were treated with sorafenib prior to disease progression.

The primary endpoint of the study was progression-free survival (PFS); further endpoints were overall survival as well as endpoints on health status, health-related quality of life, and adverse events.

Regarding the similarity of the studies and the relevant sub-population for indirect comparison

The SELECT and DECISION studies are sufficiently comparable, particularly with regard to their design as well as the demographic and clinical characteristics of the patients.

However, the proportion of patients receiving follow-up therapy differs between the two studies. In the intervention arm of the DECISION study 27% of patients at the primary data cut-off and 42% at the final data cut-off continued to receive treatment with sorafenib, even after disease progression. In the SELECT study, further treatment with lenvatinib in the intervention arm after progression was not planned, but no restrictions were placed on follow-up therapies. After completing the study medication, only a few patients received follow-up therapy (for the primary data cut-off, 16% in the lenvatinib arm and 12% in the placebo arm (without lenvatinib)). However, this difference does not fundamentally call into question the comparability of the studies.

In contrast to the DECISION study, the SELECT study also included patients who had already received therapy targeted against VEGF/VEGFR. This was the case for 25.3% of the

patients in the lenvatinib arm and 20.6% of the patients in the placebo arm. In order to improve the comparability of the study population, these patients were not used by the pharmaceutical company for the adjusted indirect comparison.

Regarding the results of the indirect comparison presented

No suitable data from the DECISION and SELECT studies are available to indirectly compare lenvatinib with sorafenib. There is therefore no way of indirectly comparing lenvatinib and sorafenib to establish an additional benefit for the present benefit assessment.

In the mortality category, the data available on the endpoint overall survival show such uncertainty that no valid conclusions can be drawn about the additional benefit of lenvatinib compared with sorafenib. Because in both studies a high proportion of patients moved from the placebo arm to the intervention arm after disease progression (SELECT: 88% at the data cut-off of 15 June 2014; DECISION: 77% at the final data cut-off of 30 August 2017), the endpoint-specific risk of bias for overall survival results is assessed as high for both studies.

To avoid this bias because of the high proportions of patients switching treatment, the pharmaceutical company adjusted the results using Rank Preserving Structural Failure Time Models (RPSFTM). However, only the SELECT study seems to have planned for such an adjustment in advance in the study protocol. Because the RPFSTM is based on restrictive model assumptions, it can be assumed that the results have only a low degree of certainty. At present, there are no adjustment methodologies that can statistically model switching with a reliable degree of certainty. Thus, the inherently significant uncertainties associated with treatment switching are likely to severely bias the adjusted analyses of the overall survival endpoint.

In the categories morbidity and health-related quality of life, data are available only for the DECISION study. Thus, no data are available for indirect comparison in these categories.

For the endpoints in the category side effects, the pharmaceutical company has not presented time-adjusted analyses for indirect comparison but rather evaluations based on the proportion of patients with event. Because in both studies there was a clear difference in the median treatment duration between the study arms (SELECT: 13.8 vs 3.9 months; DECISION: 10.6 vs 6.5 months), these evaluations cannot be used to derive valid statements on the additional benefit of lenvatinib compared with sorafenib because of the insufficient certainty of the results.

Summary

No suitable data are available to perform an adjusted indirect comparison between lenvatinib and sorafenib from the DECISION and SELECT studies. The indirect comparison can therefore not be used to derive an additional benefit for the present assessment.

In the category mortality, the data for indirect comparison with the endpoint overall survival are so uncertain because of the high proportion of patients switching from the control arm to the intervention arm that no valid statements can be derived about the additional benefit of lenvatinib compared with sorafenib. In the categories morbidity and health-related quality of life, only one side of the indirect comparison (DECISION study) offers data for an indirect comparison. In the category side effects, the evaluations submitted by the pharmaceutical company cannot be used because of the insufficient certainty of results.

An additional benefit of lenvatinib as a monotherapy in adult patients with progressive, locally advanced, or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC) that has not responded to radioactive iodine therapy (RAI) is therefore not proven compared with sorafenib.

2.1.4 Summary of the assessment

The present assessment concerns the renewed benefit assessment of the active ingredient lenvatinib following the withdrawal of orphan drug status in the following therapeutic indication:

“LENVIMA is indicated as monotherapy for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)”.

Sorafenib was determined as an appropriate comparator therapy by the G-BA:

To support its claim of an additional benefit, the pharmaceutical company submitted an adjusted indirect comparison of the randomised, double-blind, controlled phase III studies SELECT (lenvatinib vs placebo) and DECISION (sorafenib vs placebo) via the bridge comparator placebo. The SELECT study included adult patients with histologically or cytologically confirmed diagnosis of a DTC (papillary, follicular, or Hürthle cell), and the DECISION study included adult patients with histologically or cytologically confirmed diagnosis of a DTC (papillary, follicular, Hürthle cell, or poorly differentiated).

In the category mortality, the data submitted on the endpoint overall survival are so uncertain because of the high proportion of patients switching from the control arm to the intervention arm that no valid statements can be derived about the additional benefit of lenvatinib compared with sorafenib.

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

In the category side effects, the evaluations submitted by the pharmaceutical company cannot be used because of the insufficient certainty of results.

Overall, there are no suitable data from the DECISION and SELECT studies to form an adjusted indirect comparison between lenvatinib and sorafenib. This indirect comparison can therefore not be used to derive an additional benefit. An additional benefit of lenvatinib compared with sorafenib 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 bases its resolution on the information from the dossier of the pharmaceutical company. The derivation of patient numbers is comprehensible in principle but is also subject to uncertainties.

In particular, the proportion of patients with progressive thyroid carcinoma was slightly underestimated because patients whose progression only became known with the death certificate were not considered. In addition, the mortality rate for patients with thyroid carcinoma and progression, which is based on the assumption of a median survival of around four years, is set quite low in the dossier. An underestimation can therefore be assumed. However, it should be noted that patients in this indication are expected to have a lower survival rate because of the lack of RAI response.

The ranges used here take into account uncertainties in the data basis and reflect the minimum and maximum values obtained when deriving the patient numbers. Because of the uncertainties in the data basis, a more precise indication of the target population is not possible.

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 Lenvima® (active ingredient: lenvatinib) at the following publicly accessible link (last access: 9 May 2019):

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

Only specialists in internal medicine, haematology, and oncology with experience treating patients with thyroid cancer, specialists in internal medicine and endocrinology, and other doctors from other specialisms participating in the oncology agreement after consultation with a specialist in nuclear medicine may initiate and monitor treatment with lenvatinib.

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 July 2019).

Treatment period:

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.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Lenvatinib	continuous, 1 × daily	365	1	365
Appropriate comparator therapy				
Sorafenib	continuous, 2 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/application	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/patient/year	Average annual consumption by potency
Medicinal product to be assessed					
Lenvatinib	24 mg	24 mg	2 × 10 mg + 1 × 4 mg	365	730 × 10 mg + 365 × 4 mg
Appropriate comparator therapy					
Sorafenib	400 mg	800 mg	4 × 200 mg	365	1460 × 200 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 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 pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package 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					
Lenvatinib 10 mg	30 HC	€ 2,214.55	€ 1.77	€ 123.20	€ 2,089.58
Lenvatinib 4 mg	30 HC	€ 2,214.55	€ 1.77	€ 123.20	€ 2,089.58
Appropriate comparator therapy					
Sorafenib	112 FCT	€ 4,874.32	€ 1.77	€ 275.10	€ 4,597.45
Abbreviations: FCT = film-coated tablets, HC = hard capsules					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 July 2019

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 usual expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

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

In a letter dated 20 September 2018, received on 20 September 2018, the pharmaceutical company requested consultation in accordance with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) on, among other things, the question of appropriate comparator therapy. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 November 2018. The consultation meeting took place on 6 December 2018.

On 14 February 2019, the pharmaceutical company submitted a dossier for benefit assessment to the G-BA in due time (i.e. within three months after receipt of the request of the G-BA) in corresponding application of Section 35a, paragraph 1, sentence 11 SGB V in conjunction with Chapter 5, Section 8, number 6 and Section 12, number 2 of the Rules of Procedure (VerfO) of the G-BA.

By letter dated 15 February 2019 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 lenvatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 May 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 May 2019. The deadline for submitting written statements was 5 June 2019.

The oral hearing was held on 24 June 2019.

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 23 July 2019, and the proposed resolution was approved.

At its session on 15 August 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	27 November 2018	Determination of the appropriate comparator therapy
Working group Section 35a	18 June 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	24 June 2019	Conduct of the oral hearing
Working group Section 35a	3 July 2019 17 July 2019	Consultation on the dossier assessment by the IQWiG and the evaluation of the written statement procedure
Subcommittee Medicinal product	23 July 2019	Concluding discussion of the proposed resolution
Plenum	15 August 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 August 2019

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

Prof Hecken