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 Lenvatinib (new therapeutic indication: endometrial carcinoma, after prior platinum-containing therapy, combination with pembrolizumab)

of 7 July 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 active ingredient lenvatinib (Lenvima) was listed for the first time on 1 July 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 26 November 2021, lenvatinib 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 European 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 7 December 2021, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 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 lenvatinib with the new therapeutic indication: "Lenvatinib in combination with pembrolizumab is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation."

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 19 April 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 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, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by 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 lenvatinib.

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 Lenvatinib (Lenvima) in accordance with the product information

Lenvatinib in combination with pembrolizumab is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.

Therapeutic indication of the resolution (resolution of 07.07.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation

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

Appropriate comparator therapy for Lenvatinib in combination with pembrolizumab:

Therapy according to doctor's instructions

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. In addition to lenvatinib, the following active ingredients are approved for the present therapeutic indication: Cisplatin, dostarlimab, doxorubicin, medroxyprogesterone acetate, megestrol acetate and pembrolizumab.

on 2. A non-medicinal treatment does not come into question for the present therapeutic indication.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Dostarlimab - resolution of 2 December 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 therapeutic indication according to Section 35a paragraph 7 SGB V.

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 provision.

The available evidence indicates, among others, systemic chemotherapy, which can also be a platinum-containing re-therapy for the present treatment situation. According to the authorisation status, the active ingredients cisplatin and doxorubicin can be considered for this purpose. In addition, the guidelines recommend chemotherapy with carboplatin in combination with paclitaxel. Furthermore, according to the explanations of the scientific-medical societies in previous benefit assessment procedures, monotherapy with paclitaxel represents a relevant treatment option in the therapeutic indication.

The active ingredients carboplatin and paclitaxel are not approved for the present indication. There is a discrepancy between medicinal products approved in the indication and those used in health care/recommended by the guidelines.

Furthermore, according to guidelines and statements of the scientific-medical societies, endocrine therapy can be considered as a treatment option for the present treatment situation.

Taking into account the advanced stage of the disease and treatment, the G-BA also considers best supportive care to be a treatment option.

In addition, on 21 April 2021, dostarlimab was approved as monotherapy for the treatment of mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial carcinoma that has progressed on or following prior treatment with a platinum-based therapy. In its resolution of 2 December 2021, the G-BA, against the background that no suitable study data were available for the benefit assessment, did not determine an additional benefit of dostarlimab in this therapeutic indication compared with the appropriate comparator therapy. Dostarlimab is currently not considered to be an appropriate comparator therapy.

Pembrolizumab (in combination with lenvatinib) has also been approved for this therapeutic indication since 15 November 2021. The active ingredient is currently undergoing a parallel benefit assessment procedure corresponding to the present benefit assessment. Against this background, this combination cannot be considered as an appropriate comparator therapy.

Overall, the G-BA determines a therapy according to the doctor’s instructions as an appropriate comparator therapy on the basis of the underlying evidence.

As part of the therapy according to the doctor's instructions, endocrine therapy with the active ingredients medroxyprogesterone acetate, megestrol acetate as well as systemic chemotherapy, which can also be platinum-containing re-therapy, with

cisplatin (monotherapy or in combination with doxorubicin), doxorubicin (monotherapy or in combination with cisplatin), paclitaxel (monotherapy) as well as carboplatin in combination paclitaxel and best supportive care alone are considered appropriate comparators.

Best Supportive Care (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

For the implementation of the therapy according to the doctor's instructions, the comparison for the benefit assessment should include several of the above-mentioned treatment options and adequately represent the therapies frequently used in the reality of care in Germany. The choice of comparators used must be justified in the dossier for the benefit assessment. Considering the number of treatment options available in the context of therapy according to the doctor's instructions, a single-comparator comparison does not appear to be appropriate. However, this procedure would have to be justified separately should only a single-comparator comparison be carried out.

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 in combination with pembrolizumab is assessed as follows:

There is indication of a considerable additional benefit of lenvatinib in combination with pembrolizumab.

Justification:

For the proof of additional benefit of lenvatinib in combination with pembrolizumab, the pharmaceutical company presented the results of the KEYNOTE 775 / 309 study.

KEYNOTE 775 / 309 is a multicentre, open-label, randomised controlled study comparing lenvatinib in combination with pembrolizumab with a therapy according to doctor's instructions under selection of doxorubicin or paclitaxel. The study enrolled adult patients with advanced or recurrent endometrial carcinoma and disease progression after prior systemic platinum-based chemotherapy. Patients were allowed to have received a maximum of 2 prior platinum-based chemotherapies as long as 1 of them was neoadjuvant or adjuvant. In addition, patients were allowed to have received a maximum of 1 prior systemic chemotherapy, while neoadjuvant or adjuvant administrations were excluded. There were no limitations regarding hormone therapy prior to the time of enrolment in the study. Patients with disease progression during a prior platinum-based therapy were not enrolled in the study.

Furthermore, patients should have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1 for enrolment in the study.

The 827 patients enrolled were randomised 1:1 to treatment with lenvatinib + pembrolizumab (N = 411) or to therapy according to doctor's instructions (N = 416, of which doxorubicin N = 307 and paclitaxel N = 109). Prior to randomisation, the principal investigator determined which of the two options the respective patient should be treated with in the event of randomisation to the comparator arm.

It was first stratified by mismatch repair (MMR) status (proficient [pMMR] vs deficient [dMMR]). Within the pMMR stratum, further stratification was done by ECOG-PS (0 vs 1), geographical region (Europe, USA, Canada, Australia, New Zealand, Israel vs rest of the world) and prior pelvic radiotherapy (yes vs no).

Treatment was given in the KEYNOTE 775 / 309 study until confirmed disease progression, unacceptable toxicity or withdrawal of consent. Additional discontinuation criteria were treatment to completion of a maximum of 24-month therapy for pembrolizumab and a cumulative lifetime dose of 500 mg/m² body surface area for doxorubicin.

The KEYNOTE 775 / 309 study was conducted in 167 study sites across Asia, Australia, Europe, North America and South America. The study was launched in June 2018 and is currently ongoing.

In the dossier for the benefit assessment, the pharmaceutical company submitted the data cut-off from 26.10.2020. This is the 1st interim analysis for overall survival pre-specified after approximately 368 deaths in the study population with pMMR status and at least 6 months after randomisation of the last patient. At the time of submission of the dossier for the benefit assessment, the final analysis for overall survival, which was planned after approximately 526 deaths in the study population with pMMR status and at least 18 months after randomisation of the last patient, was not yet available. This took place on 1 March 2022.

As part of the written statement procedure on the present benefit assessment, the pharmaceutical company additionally submitted the results of the final analysis from 1 March 2022. No subgroup analyses were available for these evaluations. Furthermore, the data are assessed by the G-BA to the effect that there are no significantly new findings for the benefit assessment compared to the interim analysis of 26.10.2020. For the present benefit assessment, the results of the interim analysis of 26.10.2020 are used.

About the patient population relevant for the benefit assessment

For the present benefit assessment procedure, the G-BA adjusted the appropriate comparator therapy at short notice prior to the start of the procedure. Here, paclitaxel as monotherapy was added as an additional treatment option as part of the therapy according to the doctor's instructions.

In the dossier for the benefit assessment, the pharmaceutical company submitted an evaluation for the sub-population of patients in the KEYNOTE 775 / 309 study, for whom a therapy with doxorubicin was selected by the principal investigator prior to randomisation, taking into account the originally determined appropriate comparator therapy. As part of the written statement procedure on the present benefit assessment, the pharmaceutical company submitted the results of the total population of the KEYNOTE 775 / 309 study as well as corresponding subgroup analyses for the data cut-off of 26.10.2020, taking into account the adjustment of the appropriate comparator therapy.

Against the background of the comparison made in the study with a therapy according to doctor's instructions under selection of doxorubicin or paclitaxel, the data on the total population of the study are used for the benefit assessment.

Implementation of the appropriate comparator therapy

In IQWiG's dossier assessment, a separate assessment of the additional benefit was made for patients for whom doxorubicin or paclitaxel is the appropriate or inappropriate therapy according to doctor's instructions. This was done against the background that, in addition to doxorubicin and paclitaxel, other treatment options are included in the appropriate comparator therapy (therapy according to doctor's instructions) - such as endocrine therapy, platinum-based re-therapy or exclusive BSC therapy. However, according to IQWiG's dossier assessment, the KEYNOTE 775 / 309 study does not allow any conclusions to be drawn about the additional benefit for patients for whom a treatment option other than doxorubicin or paclitaxel is the appropriate therapy according to doctor's instructions.

In accordance with the above explanations on the appropriate comparator therapy, the therapy according to doctor's instructions should include several of the above-mentioned treatment options and adequately represent the therapies frequently used in the reality of health care in Germany. Taking into account the available statements of the scientific-medical societies and clinical experts on the significance of the different treatment options in the reality of care, the G-BA considers the comparison with doxorubicin or paclitaxel in the context of a therapy according to doctor's instructions for the present benefit assessment of lenvatinib in combination with pembrolizumab to be appropriate in order to assess the additional benefit for the patient population according to the therapeutic indication. A separate statement on the additional benefit for patients for whom doxorubicin or paclitaxel is the appropriate or inappropriate therapy according to medical criteria is therefore not made in the present assessment.

Extent and probability of the additional benefit

Mortality

Overall survival is defined in the KEYNOTE 775 / 309 study as the time between randomisation and death, regardless of the underlying cause of death.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of lenvatinib in combination with pembrolizumab. This prolongation of survival time by treatment with lenvatinib in combination with pembrolizumab compared to treatment with the appropriate comparator therapy is assessed as a significant improvement.

Morbidity

Progression-free survival (PFS)

Progression-free survival is defined in the KEYNOTE 775 / 309 study as the time between randomisation and disease progression (determined using RECIST criteria version 1.1) or death, regardless of the underlying cause of death.

Prolongation of PFS was statistically significant in the intervention arm compared to the control arm.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" was not assessed in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST criteria). Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS.
The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology

Symptomatology is assessed in the KEYNOTE 775 / 309 study using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the disease-specific additional module for endometrial carcinoma EORTC QLQ-EN24.

As part of the written statement procedure on the present benefit assessment, the pharmaceutical company submitted continuous evaluations (mean value differences compared to the start of the study) for the overall population of the study for this endpoint. These are used for the present benefit assessment.

For the endpoints of fatigue, nausea and vomiting, constipation and urological symptoms, there was a statistically significant difference to the advantage of lenvatinib in combination with pembrolizumab. In order to assess the relevance of the results, the standardised mean difference (SMD) in terms of Hedges' g is used. The 95% confidence interval of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

For the endpoints of appetite loss and muscular pain, there was a statistically significant difference to the disadvantage of lenvatinib in combination with pembrolizumab in each case. The 95% confidence interval of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

For the endpoints of dyspnoea, lymphoedema, tingling/ numbness, change in taste and hair loss, there was a statistically significant difference to the advantage of lenvatinib in combination with pembrolizumab. The 95% confidence interval of the SMD was completely outside the irrelevance range of -0.2 to 0.2. This is interpreted as a relevant effect.

For the endpoint of diarrhoea, there was a statistically significant difference to the disadvantage of lenvatinib in combination with pembrolizumab. Again, the 95% confidence interval of the SMD was completely outside the irrelevant range of -0.2 to 0.2, so this is interpreted as a relevant effect.

No usable data were available for the endpoint of sexual/ vaginal disorders, as only 18.4% of patients were included in the evaluation.

For all other endpoints, no statistically significant difference was detected between the study arms.

In summary, treatment with lenvatinib in combination with pembrolizumab has positive effects on several symptomatology endpoints and a negative effect on the diarrhoea endpoint. In the overall assessment of the results, there is an advantage of lenvatinib in combination with pembrolizumab with regard to symptomatology.

Health status (EQ-5D, visual analogue scale)

General health status is assessed in the KEYNOTE 775 / 309 study using the EQ-5D visual analogue scale (VAS).

The pharmaceutical company submitted continuous evaluations (mean differences compared to the start of the study) for this endpoint, which are used for the present benefit assessment.

For the endpoints of health status, there was a statistically significant difference to the advantage of lenvatinib in combination with pembrolizumab. The 95% confidence interval of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

Thus, there are neither positive nor negative effects of lenvatinib in combination with pembrolizumab with regard to the health status.

Quality of life

Health-related quality of life is assessed in the KEYNOTE 775 / 309 study using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the disease-specific additional module for endometrial carcinoma EORTC QLQ-EN24.

The pharmaceutical company submitted continuous evaluations (mean differences compared to the start of the study) for this endpoint, which are used for the present benefit assessment.

For the endpoints of emotional functioning and social functioning, there was a statistically significant difference to the advantage of lenvatinib in combination with pembrolizumab. The 95% confidence interval of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

For the endpoint of negative body image, there was a statistically significant difference to the advantage of lenvatinib in combination with pembrolizumab. The 95% confidence interval of the SMD was completely outside the irrelevance range of -0.2 to 0.2. This is interpreted as a relevant effect.

No usable data were available for the sexual enjoyment endpoint, as only 18.2% of patients were included in the evaluation.

For all other endpoints, no statistically significant difference was detected between the study arms.

In the overall analysis, only one endpoint showed a significant difference between the treatments: positive effect in the endpoint "negative body image". Against the background of the different aspects of health-related quality of life that were examined in the study using the EORTC QLQ-C30 and EORTC QLQ-EN24 questionnaires, this one effect is not considered sufficient to be able to assume an overall improvement in health-related quality of life.

Side effects

Adverse events (AEs)

In the KEYNOTE 775 / 309 study, AEs occurred in both study arms in almost all patients. The results were only presented additionally.

Serious adverse events (SAE)

For serious adverse events, there was a statistically significant difference to the disadvantage of lenvatinib in combination with pembrolizumab.

Severe AE (CTCAE grade ≥ 3)

For serious adverse events with CTCAE grade ≥ 3, there was no statistically significant difference between the study arms.

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, there was a statistically significant difference to the disadvantage of lenvatinib in combination with pembrolizumab.

Specific AEs

For the specific AEs of immune-mediated SAEs, immune-mediated severe AEs, hypertension (PT, severe AEs), headache (PT, AEs), urinary tract infection (PT, SAEs), gastrointestinal disorders (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs), lipase elevated (PT, severe AEs), weight loss (PT, severe AEs), metabolism and nutrition disorders (SOC, serious AEs), musculoskeletal and connective tissue disorders (SOC, serious AEs), proteinuria (PT, serious AEs) and palmar-plantar erythrodysesthesia syndrome (PT, serious AEs), there was a statistically significant difference to the disadvantage of lenvatinib in combination with pembrolizumab.

For the specific AE of alopecia (PT, AEs), blood and lymphatic system disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs), there was a statistically significant difference to the advantage of lenvatinib in combination with pembrolizumab.

For the specific AE of cardiotoxicity (SOC, severe AEs), there was no statistically significant difference between the study arms.

The palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) is of particular relevance among the specific severe AEs that occur more frequently during treatment with lenvatinib in combination with pembrolizumab. This is described as a very distressing side effect for patients and is a known side effect of lenvatinib therapy.

According to the explanations of the scientific-medical societies in the written statement procedure on the present benefit assessment, the side effects occurring with lenvatinib in combination with pembrolizumab, such as hypertension, weight loss or diarrhoea, were also pointed out; in addition, according to clinical experts, there was a high rate of hypothyroidism as a result of overlapping side effects. Overall, according to the scientific-medical societies, the high rate of side effects makes careful management of side effects necessary.

In summary, in terms of side effects, a disadvantage of treatment with lenvatinib in combination with pembrolizumab can be identified due to the negative effects in serious AEs and therapy discontinuations due to AEs. With regard to specific adverse events, there were, in detail, predominantly disadvantages of lenvatinib in combination with pembrolizumab.

Overall assessment

For the benefit assessment of lenvatinib in combination with pembrolizumab, data from the open-label, randomised controlled KEYNOTE 775 / 309 study on mortality, morbidity, quality of life and side effects are available.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of lenvatinib in combination with pembrolizumab. The magnitude of the effect is assessed as a significant improvement.

With regard to symptomatology (assessed using EORTC QLQ-C30 and -EN24), therapy with lenvatinib in combination with pembrolizumab showed positive effects with regard to the endpoints of dyspnoea, lymphoedema, tingling/ numbness, change in taste and hair loss, and a negative effect with regard to the endpoint of diarrhoea. In terms of symptomatology, there is an advantage of lenvatinib in combination with pembrolizumab in the overall assessment. With regard to health status (assessed by EQ-5D VAS), there are neither positive nor negative effects.

For the health-related quality of life (assessed by means of EORTC QLQ-C30 and -EN24), there is no improvement in the overall assessment of all results.

In terms of side effects, there are disadvantages of lenvatinib in combination with pembrolizumab for serious AEs and therapy discontinuations due to AEs. There were no statistically significant differences between the study arms in terms of severe AEs. In detail, the specific AEs show predominantly negative effects of lenvatinib in combination with pembrolizumab.

The overall results show a significant improvement in overall survival. In addition, there are predominantly advantages in terms of symptomatology. In contrast, there are disadvantages in the case of serious AEs and therapy discontinuations due to AEs.

As a result, a considerable additional benefit is identified for lenvatinib in combination with pembrolizumab compared to the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, open-label, controlled phase III KEYNOTE 775 / 309 study. At the study level, the risk of bias is considered low.

For the endpoint of overall survival, there is also a low risk of bias.

For the endpoints in the areas of symptomatology, health status and health-related quality of life, the risk of bias is classified as high due to the lack of blinding. Furthermore, the strong decline in the returns of the questionnaires and the clearly different durations of observation between the study arms contribute to this for these endpoints.

It should also be taken into account that the uncertainties presented in IQWiG's dossier assessment with regard to the dosage of paclitaxel used in the study, which is not approved in the indication relevant to the assessment, were not confirmed by the clinical experts in the written statement procedure for the present benefit assessment. According to clinical experts, the selected dosing scheme with treatment break in week 4 of each 28-day cycle is an appropriate dosing scheme.

Overall, the available data basis is subject to uncertainties. However, these uncertainties are not rated to be so high as to justify a downgrading of the reliability of data of the overall assessment. In particular, the risk of bias of the endpoint of overall survival is rated as low.

Thus, the reliability of data of the additional benefit identified is classified in the "indication" category.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient lenvatinib:

"Lenvatinib in combination with pembrolizumab is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation."

The appropriate comparator therapy was determined by G-BA to be a therapy according to doctor's instructions".

The pharmaceutical company presents the results of the open-label, randomised, controlled KEYNOTE 775 / 309 study, in which lenvatinib + pembrolizumab is compared with a therapy according to doctor's instructions under selection of doxorubicin or paclitaxel.

For the endpoint of overall survival, there is a statistically significant advantage of lenvatinib + pembrolizumab, which was assessed as a significant improvement.

For symptomatology, there are advantages of lenvatinib + pembrolizumab for dyspnoea, lymphoedema, tingling/ numbness, change in taste and hair loss, and a disadvantage for the endpoint of diarrhoea. There is no difference with regard to health status.
In the overall assessment of all results, there is no improvement for the health-related quality of life.

In terms of side effects, there are disadvantages of lenvatinib + pembrolizumab for SAEs and discontinuation due to AEs. In detail, the specific AEs predominantly show disadvantages.

Overall, especially in view of the lack of blinding, the data basis is fraught with uncertainties. However, these are not rated to be so high as to justify a downgrading of the reliability of data of the overall assessment.

As a result, the G-BA found an indication of a considerable additional benefit of lenvatinib + pembrolizumab compared with the appropriate comparator therapy.

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).

Against the background that the data on the number of patients submitted by the pharmaceutical company in the dossier are subject to uncertainties, the G-BA based its resolution on the data from IQWiG's dossier assessment. These represent an overall range that can be derived, taking into account the information in the dossier on the parallel benefit assessment procedure for pembrolizumab in combination with lenvatinib. It must be taken into account that uncertainty must also be assumed for this range.

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: 5 May 2022):

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

Therapy with lenvatinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with endometrial carcinoma.

In the KEYNOTE 775 / 309 study, treatment with lenvatinib in combination with pembrolizumab was compared with treatment according to doctor's instructions under selection of doxorubicin or paclitaxel only. No comparison was made with other treatment options.

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 June 2022).

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.

Best supportive care

The treatment costs for best supportive care are different for each individual patient. Because best supportive care has been determined as an 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.

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	1 x daily	365	1	365
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Therapy according to doctor's instructions[a]				
Medroxyprogesterone acetate	1 – 3 x daily	365	1	365
Megestrol acetate	1 x daily	365	1	365
Cisplatin monotherapy				
Cisplatin	1 x per 21–28-day cycle	13.0 – 17.4	1	13.0 – 17.4
	or			
	Day 1 – 5 per 21–28-day cycle	13.0 – 17.4	5	65.0 – 87.0
Doxorubicin monotherapy				
Doxorubicin	1 x per 21-day cycle	7	1	7
Cisplatin + doxorubicin[2]				
Cisplatin	1 x per 21-day cycle	6	1	6
Doxorubicin	1 x per 21-day cycle	6	1	6
Best supportive care	Different from patient to patient			

[2] Nomura H et al.: Japanese Gynaecologic Oncology Group. Effect of Taxane Plus Platinum Regimens vs Doxorubicin Plus Cisplatin as Adjuvant Chemotherapy for Endometrial Cancer at a High Risk of Progression: A Randomised Clinical Trial. JAMA Oncol. 2019 Jun 1;5(6):833-840. doi: 10.1001/jamaoncol.2019.0001.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
[a] The active ingredients carboplatin and paclitaxel are suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.				

Consumption:

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.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The product information on medroxyprogesterone acetate specifies the most common dosage of 300 - 600 mg per day for the treatment of endometrial carcinoma. A dosage of 250 mg - 500 mg is presented for the present calculation.

The study by Nomura et al. (2019)[3] is used to calculate the dosage of the combination therapy of cisplatin and doxorubicin.

The average body measurements were applied for dosages depending on body weight (BW) or body surface area (BSA), (average body height of an adult female: 1.66 m, average body weight of an adult female: 68.7 kg). This results in a body surface area of 1.76 m² (calculated according to Du Bois 1916)[4]

The maximum cumulative total dose of doxorubicin is 450 - 550 mg/m^2 BSA. On this basis, an approximate treatment duration of 7 cycles is used for monotherapy with doxorubicin.

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					
Lenvatinib	20 mg	20 mg	2 x 10 mg	365	730 x 10 mg

[3] Nomura H et al.: Japanese Gynaecologic Oncology Group. Effect of Taxane Plus Platinum Regimens vs Doxorubicin Plus Cisplatin as Adjuvant Chemotherapy for Endometrial Cancer at a High Risk of Progression: A Randomised Clinical Trial. JAMA Oncol. 2019 Jun 1;5(6):833-840. doi: 10.1001/jamaoncol.2019.0001.

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Therapy according to doctor's instructions[a]					
Medroxyprogesterone acetate	125 mg – 250 mg	300 mg – 600 mg	1 x 250 mg + 1 x 500 mg	365	365 x 250 mg + 365 x 500 mg
Megestrol acetate	80mg - 320mg	80mg - 320mg	0.5 x 160 mg[5] + 2 x 160 mg	365	182.5 x 160 mg – 730 x 160 mg
Cisplatin monotherapy					
Cisplatin	50 mg/m² – 120 mg/m² = 88.0 mg - 211.2 mg	88.0mg - 211.2mg	1 x 100 mg – 2 x 100 mg + 2 x 10 mg	13.0 – 17.4	(13.0 x 100 mg – 26.0 x 100 mg + 26.0 x 10 mg) – 17.4 x 100 mg – 34.8 x 100 mg + 34.8 x 10 mg)
	or				
	15 mg/m² – 20 mg/m² = 26.4 mg – 35.2 mg	26.4 mg – 35.2 mg	1 x 50 mg – 1 x 50 mg	65.0 – 87.0	65.0 x 50 mg – 87.0 x 50 mg
Doxorubicin monotherapy					
Doxorubicin	60 mg/m² = 105.6 mg – 75 mg/m² = 132 mg	105.6 mg – 132 mg	1 x 100 mg + 1 x 10 mg - 1 x 150 mg	7	7 x 100 mg + 7 x 10 mg – 7 x 150 mg

[5] As of 15.05.2022, megestrol acetate is only available on the German market in 160 mg pack, which is why a division of the tablets must be assumed here in exceptional cases. The tablets can be divided into equal doses.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cisplatin + doxorubicin					
Cisplatin	50 mg/m^2 body surface area = 88 mg	88 mg	1 x 100 mg	6	6 x 100 mg
Doxorubicin	60 mg/m^2 = 105.6 mg	105.6 mg	1 x 100 mg + 1 x 10 mg	6	6 x 100 mg + 6 x 10 mg
Best supportive care	Different from patient to patient				
[a] The active ingredients carboplatin and paclitaxel are suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.					

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					
Lenvatinib 10 mg	30 HC	€ 1,853.45	€ 1.77	€ 102.56	€ 1,749.12
Pembrolizumab 100 mg	1 CIS	€ 3,037.30	€ 1.77	€ 170.17	€ 2,865.36
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Cisplatin 100 mg	1 CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68

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
Cisplatin 50 mg	1 CIS	€ 47.70	€ 1.77	€ 4.61	€ 41.32
Cisplatin 10 mg	1 CIS	€ 17.49	€ 1.77	€ 0.30	€ 15.42
Doxorubicin 150 mg[6]	1 SFI	€ 418.32	€ 1.77	€ 32.19	€ 384.36
Doxorubicin 100 mg[6]	1 CIS	€ 285.75	€ 1.77	€ 21.71	€ 262.27
Doxorubicin 10 mg[6]	1 CIS	€ 40.28	€ 1.77	€ 2.29	€ 36.22
Medroxyprogesterone acetate 500 mg	100 TAB	€ 355.73	€ 1.77	€ 19.07	€ 334.89
Medroxyprogesterone acetate 250 mg	50 TAB	€ 104.80	€ 1.77	€ 5.18	€ 97.85
Megestrol acetate 160 mg	84 TAB	€ 1,154.18	€ 1.77	€ 63.28	€ 1,089.13
Best supportive care	Different from patient to patient				
Abbreviations: HC = hard capsules, SFI = solution for injection, CIS = concentrate for the preparation of an infusion solution, TAB = tablets					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be 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.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I to the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

[6] Fixed reimbursement rate

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	Treatment days/ year	Costs/ patient/ year
Cisplatin							
Antiemetic treatment							
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information does not provide any specific information why the necessary costs cannot be quantified.							
Hydration/ diuresis							
Cisplatin (monotherapy)							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	13.0 - 17.4 or 65.0 – 87.0	€ 118.43 - € 158.51 or € 592.15 – 792.57
Sodium chloride 0.9% infusion solution, 3 l - 4,4 l/day	10 x 1000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	13.0 - 17.4 or 65.0 – 87.0	(€ 127.06 - € 196.57) - (€ 170.07 - € 263.11) or (€ 635.31 - € 850.34) – € 982.87 - € 1,315.53)
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Cisplatin (combination therapy)							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	6	€ 91.10
Sodium chloride 0.9% infusion solution, 3 l - 4,4 l/day	10 x 1000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	6	€ 65.16 - € 97.74

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory

services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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 26 January 2021, 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 07 December 2021.

On 7 December 2021 the pharmaceutical company submitted a dossier for the benefit assessment of lenvatinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

By letter dated 8 December 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 lenvatinib. In a letter dated 22 December 2021, the G-BA informed IQWiG about the prolongation of the benefit assessment procedure agreed in the Subcommittee on Medicinal Products on 21 December 2021.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 April 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 19 April 2022. The deadline for submitting written statements was 10 May 2022.

The oral hearing was held on 23 May 2022.

By letter dated 24 May 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 15 June 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 28 June 2022, and the proposed resolution was approved.

At its session on 7 July 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 January 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	7 December 2021	New determination of the appropriate comparator therapy
Subcommittee Medicinal products	21 December 2021	Prolongation of the benefit assessment procedure determined
Working group Section 35a	18 May 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	23 May 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	1 June 2022 22 June 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	28 June 2022	Concluding discussion of the draft resolution
Plenum	7 July 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 7 July 2022

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

Prof. Hecken