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)
Cemiplimab (new therapeutic indication:
cervical cancer, pretreated)

of 19 October 2023

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 cemiplimab (Libtayo) was listed for the first time on 1 August 2019 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 7 June 2022, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for Cemiplimab in the therapeutic indication in question here "recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy" in accordance with Section 35a paragraph 5b SGB V.

At its session on 21 July 2022, the G-BA approved the application to postpone the relevant date in accordance with Section 35a, paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question here to four weeks after the marketing authorisation

of the additional therapeutic indication covered by the application, at the latest six months after the first relevant date. The marketing authorisation of the additional therapeutic indication "first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 1% tumour cells), with no EGFR, ALK or ROS1 aberrations" covered by the application according to Section 35a paragraph 5b SGB V was granted within the 6-month period.

For the therapeutic indication in question here "recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy", cemiplimab received the extension of the marketing authorisation as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) number 1234/2008 of the Commission from 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, sentence 7) on 18 November 2022. In accordance with the resolution of 21 July 2022, the benefit assessment of the active ingredient cemiplimab in this therapeutic indication thus started at the latest within four weeks of granting of the marketing authorisation of cemiplimab in the therapeutic indication on 24 March 2023 "first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 1% tumour cells), with no EGFR, ALK or ROS1 aberrations", as well as 6 months after the first relevant date, i.e. at the latest on 16 June 2023.

On 19 April 2023, the pharmaceutical company has submitted in due time a dossier in accordance with Section 4, paragraph 3, number 3 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 cemiplimab with the new therapeutic indication "recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy".

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 August 2023 on the G-BA website (www.g-ba.de), 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 cemiplimab 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 cemiplimab.

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:

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

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Cemiplimab (Libtayo) in accordance with the product information

LIBTAYO as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

Therapeutic indication of the resolution (resolution of 19.10.2023):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy

Appropriate comparator therapy:

Therapy according to doctor's instructions under selection of a monotherapy with:

- Nab-paclitaxel
- Vinorelbine
- Ifosfamide
- Topotecan
- Pemetrexed
- Irinotecan
- Pembrolizumab (for patients with PD-L1 positive cervical cancer)

b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy

Appropriate comparator therapy:

- Best supportive care

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO</u> <u>and Section 6 paragraph 2 AM-NutzenV:</u>

on 1. In addition to cemiplimab, the active ingredients bleomycin, carboplatin, cisplatin and mitomycin as well as the combination therapies bevacizumab in combination with paclitaxel and cisplatin or with paclitaxel and topotecan, ifosfamide in combination with cisplatin, pembrolizumab in combination with chemotherapy with or without bevacizumab and topotecan in combination with cisplatin are approved in the present therapeutic indication.

on 2. The use of resection and/or radiotherapy as a palliative patient-individual therapy option for symptom control depending on the localization and symptomatology of the metastases remains unaffected.

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

– Pembrolizumab: Resolution of 2 February 2023

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 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 care.

For the treatment setting after first-line therapy, monotherapy is usually recommended according to the S3 guideline "Diagnosis, therapy and after-care of patients with cervical cancer"[2] if therapy is desired. The active ingredients nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed and irinotecan are mentioned as possible therapy options. For patients with PD-L1 positive metastatic cervical cancer, pembrolizumab (monotherapy) is also mentioned as a possible therapy option in the[2,3] guidelines**.** In the S3 guideline, a phase II study is referenced for each of the aforementioned therapy options.[4,5,6,7,8,9,10]These active ingredients are not approved in the present therapeutic indication and are used off-label. According to the current S3 guideline, there are no therapy studies to date that show an improvement in overall survival for a therapy option in the case of disease progression after first-line therapy compared to best supportive care.

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[2] Guideline programme on oncology, S3 guideline Diagnostics, therapy and after-care of patients with cervical cancer, long version 2.2 - March 2022.

[3] Cibula et al.; ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer – Update 2023

[4] Alberts, D.S., et al., Phase II trial of nab-paclitaxel in the treatment of recurrent or persistent advanced cervix cancer: A gynecologic oncology group study. Gynecol Oncol, 2012. 127(3): p. 451-5.

[5] Muggia, F.M., et al., Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol, 2004. 92(2): p. 639-43.

[6] Sutton, G.P., et al., A phase II Gynecologic Oncology Group trial of ifosfamide and mesna in advanced or recurrent adenocarcinoma of the endometrium. Gynecol Oncol, 1996. 63(1): p. 25-7.

[7] Bookman, M.A., et al., Topotecan in squamous cell carcinoma of the cervix: A Phase II study of the Gynecologic Oncology Group. Gynecol Oncol, 2000. 77(3): p. 446-9.

[8] Lorusso, D., et al., Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. Ann Oncol, 2010. 21(1): p. 61-6.

[9] Verschraegen, C.F., et al., Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. J Clin Oncol, 1997. 15(2): p. 625-31.

[10] Chung, H.C., et al., Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol, 2019. 37(17): p. 1470-1478.

According to the statement of the scientific medical societies in the present benefit assessment procedure, mono-chemotherapy is currently the recommended therapy for a selected patient population in the reality of care in the case of progression after first-line systemic therapy. The statement refers to the mono-chemotherapies mentioned in the S3 guideline. The statement also notes that there are, however, no data showing a prolongation in overall survival time with chemotherapy in this setting. The treatment objective is disease control and symptom relief. According to the statement, best supportive care, which includes the use of effective cytostatic agents to alleviate symptoms, is in line with the recommendations. According to the statement, monotherapy with the checkpoint inhibitor pembrolizumab is another option for patients with PD-L1 positive metastatic cervical cancer.

In determining the appropriate comparator therapy, the G-BA took into account that recurrent or metastatic cervical cancer is a severe disease and that in the present therapeutic indication, the focus of therapy is on symptom relief and control due to the slow disease progression and the primarily local tumour activity.

For the relatively new treatment option with pembrolizumab in combination with chemotherapy with or without bevacizumab, which is approved in the present therapeutic indication, no recommendations or no recommendation for the present treatment setting and patient population are available from the guidelines and the statement of the scientific-medical societies. In view of the fact that the assessed medicinal product is used as monotherapy in the present therapeutic indication and in conjunction with the recommendations for monotherapy in the present treatment setting, pembrolizumab in combination with chemotherapy with or without bevacizumab is not considered as an appropriate comparator therapy. In addition, the use of pembrolizumab in combination with chemotherapy with or without bevacizumab is seen in first-line therapy according to the ESGO/ESTRO/ESP guideline[3].

In the overall assessment, the G-BA has determined that the appropriate comparator therapy for the present treatment setting is a therapy according to doctor's instructions with the selection of a monotherapy with nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan and pembrolizumab (for patients with PD-L1 positive cervical cancer).

Against the background of the diverse, recommended therapy options, it is expected in the present treatment setting for the implementation of the therapy according to doctor's instructions in a direct comparator study that the principal investigator has a choice of several therapy options (multicomparator study).

The monochemotherapies nab-paclitaxel, vinorelbine, pemetrexed and irinotecan as well as the checkpoint inhibitor pembrolizumab as monotherapy are not approved for the present therapeutic indication. The marketing authorisation of the active ingredients ifosfamide and topotecan is linked to the concomitant active ingredient cisplatin.

The approved treatment option pembrolizumab in combination with chemotherapy with or without bevacizumab is not considered as an appropriate comparator therapy for the aforementioned reasons.

The other approved active ingredients listed under paragraph 1 do not correspond to the therapy recommendations for the present indication and to the therapy standard in the reality of care as set out in the guidelines and in the statement of the scientific-medical societies.

In contrast, the monotherapies with nab-paclitaxel, vinorelbine, pemetrexed, irinotecan or pembrolizumab in the off-label use according to the generally accepted state of medical knowledge are thus considered to be the therapy standard for the group of patients who are eligible for further antineoplastic therapy, compared to the approved mono and combination therapies, and pursuant to Section 6, paragraph 2, sentence 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), they must generally be preferred over the medicinal products approved in the therapeutic indication according to the generally recognised state of medical knowledge. Therefore, it is appropriate to determine the above-mentioned medicinal products in the off-label use for this patient group as the appropriate comparator therapy.

The determination of the off-label use of medicinal products as an appropriate comparator therapy by resolution on the benefit assessment according to Section 35a paragraph 3 SGB V does not affect the procedure according to Section 35c SGB V.

The present therapeutic indication also includes patients who are ineligible for further antineoplastic therapy. Taking into account the statements in the guidelines and in the statement of the scientific-medical societies on the therapy recommendations and on the reality of care, this patient group is considered to be of relevant significance in the present therapeutic indication of the medicinal product to be assessed. Therefore, it is considered appropriate to address two patient groups in the appropriate comparator therapy: Patients who are eligible for further antineoplastic therapy (patient group a) and patients who are ineligible for further antineoplastic therapy (patient group b).

For the group of patients who are ineligible for further antineoplastic therapy, best supportive care is determined as the appropriate comparator therapy. "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.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

<u>Change of the appropriate comparator therapy:</u>

Originally, the appropriate comparator therapy was determined as follows:

<u>Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy</u>

– Best supportive care

This appropriate comparator therapy was determined for the present benefit assessment procedure on cemiplimab under the effects of the ruling of the Federal Social Court (FSC) of 22 February 2023. According to the FSC's comments on this ruling (file ref.: B 3 KR 14/21 R), medicinal products that do not have a marketing authorisation for the present indication and whose prescribability in off-label use has also not been recognised by the G-BA in the Pharmaceuticals Directive are generally not considered as appropriate comparator therapy in the narrower sense of Section 2, paragraph 1, sentence 3, Section 12 SGB V.

Within the scope of this provision, it was to be noted that medicinal therapies not approved for the treatment of cervical cancer with disease progression after first-line therapy are mentioned in the present guidelines or by scientific-medical societies and/or the AkdA (Drugs Commission of the German Medical Association) according to Section 35a, paragraph 7, sentence 4 SGB V.

With the entry into force of the ALBVVG (Act to Combat Supply Shortages and Improve the Supply of Medicines) on 27 July 2023, the G-BA can exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy in accordance with Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

In view of the fact that for the present benefit assessment of cemiplimab, off-label use of medicinal products can be considered as an appropriate comparator therapy, also taking into account the statements of scientific-medical societies in the present procedure, a review of the appropriate comparator therapy under the regulations after the entry into force of the ALBVVG was necessary. In the course of this, the appropriate comparator therapy was changed for the present resolution.

This change in the appropriate comparator therapy means that the results of the Empower-Cervical 1 study submitted by the pharmaceutical company in the dossier can be used for the present assessment. The Empower-Cervical 1 study was presented additionally in IQWiG's dossier assessment according to the mandate. In addition, the results of the Empower-Cervical 1 study were the subject of the statements, which is why the change in the appropriate comparator therapy does not necessitate a renewed conduct of the benefit assessment procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of cemiplimab is assessed as follows:

a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy

Indication of a considerable additional benefit.

b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy

An additional benefit is not proven.

Justification:

a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy

and

b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy

For the proof of the additional benefit of cemiplimab for patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy, the pharmaceutical company presented the results of the EMPOWER-Cervical 1 study in the dossier.

The open-label, randomised, controlled phase III EMPOWER-Cervical 1 study enrolled adult patients with recurrent or metastatic cervical cancer (squamous cell, adenocarcinoma or adenosquamous carcinoma) and disease progression on or after platinum-based chemotherapy. In the study arms, cemiplimab was compared with therapy according to doctor's instructions, selecting monotherapy with pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine (hereafter: chemotherapy). Patients had to have received prior therapy with paclitaxel and/or bevacizumab that was discontinued due to disease progression or toxicity. Patients who were ineligible for treatment with paclitaxel and/or bevacizumab, refused treatment with paclitaxel and/or bevacizumab, or did not have access to treatment with bevacizumab could be enrolled. Patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1, which corresponds to good general condition. Patients with active brain metastases were excluded from the study.

The completed study was conducted from 2017 - 2023 in 97 study sites in Asia, Australia, Europe as well as North and South America.

A total of 608 patients were randomised in the ratio 1:1 into the two study arms. 304 patients were divided into the intervention arm with cemiplimab and the control arm with chemotherapy respectively. The active ingredient for monotherapy was determined prior to randomisation. Stratification was by histology (squamous cell vs adenocarcinoma/ adenosquamous carcinoma), geographic region (North America vs Asia vs rest of the world), Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (0 or 1) and prior therapy with bevacizumab (yes vs no).

Cemiplimab was dosed at 350 mg in EMPOWER-Cervical 1 study according to the product information in a three-week cycle. Since the monotherapies of chemotherapeutic agents used in the comparator arm of the study are not approved for the present indication, no direct recommendation for the duration of treatment and the dosage results from the product information. Pemetrexed was dosed at 500 mg/m^2 body surface area (BSA) in a three-week cycle. Vinorelbine was dosed at 30 mg/m^2 BSA on day 1 and 8 of a three-week cycle. The doses and intervals of chemotherapy with pemetrexed and vinorelbine correspond to the recommendations of the S3 guideline for cervical cancer. Irinotecan was dosed at 100 mg/m^2 BSA 1x per week for 4 weeks, followed by a 10-14 day break in therapy (with the option to increase the dose to 125 mg/m^2 BSA). The guideline calls for a weekly administration of 125 mg/m^2 BSA. Topotecan was dosed at 1 mg/m^2 BSA on day 1-5 of a three-week cycle, although the guideline specifies a dose of 1.5 mg/m^2 BSA at the same interval. Irinotecan and topotecan were used at a lower dose than described in the guideline. It is not assumed that the deviations in the doses have a relevant influence on the observed effects in the EMPOWER-Cervical 1 study, as overall only approx. 20% of the patients in the comparator arm of the presented sub-population were treated with irinotecan or topotecan.

Patients were treated up to 96 weeks until disease progression, unacceptable toxicity, therapy discontinuation at one's own or doctor's discretion, or until the intended end of the study. According to the study protocol, patients from the comparator arm or patients from the

cemiplimab arm whose treatment was not yet completed can receive cemiplimab after the end of the study up to a maximum of 96 weeks as part of a cemiplimab extension phase.

The primary endpoint of the study was overall survival. Secondary endpoints are endpoints in the categories morbidity, health-related quality of life and side effects.

Data cut-offs

For the EMPOWER-Cervical 1 study, a total of 3 data cut-offs were performed:

- 1st data cut-off from 31.08.2020: pre-specified interim analysis, planned after the occurrence of 238 deaths in the group of patients with squamous cell carcinoma
- 2nd data cut-off from 04.01.2021: pre-specified interim analysis, planned after the occurrence of 289 deaths in the group of patients with squamous cell carcinoma
- 3rd data cut-off from 04.01.2022: non-prespecified analysis of overall survival, objective response rate and side effects

After the 2nd data cut-off, the study was terminated prematurely on the recommendation of the Independent Data Monitoring Committee (IDMC) due to the clear superiority of cemiplimab over chemotherapy according to the information from the pharmaceutical company. The results of this data cut-off were subsequently defined as the primary analysis and were presented in the dossier to derive the additional benefit for the relevant sub-population. This procedure is appropriate, the 2nd data cut-off is used in the following to assess all endpoints.

The 3rd data cut-off was not pre-specified and occurred as part of the marketing authorisation process, with the pharmaceutical company describing that this data cut-off was not requested by the European Medicines Agency (EMA). The results of the 3rd data cut-off are therefore not used for assessment. For the 1st data cut-off, no evaluations were presented in the dossier.

Relevant sub-population

In the dossier for the benefit assessment, the pharmaceutical company presents a sub-population from the EMPOWER-Cervical 1 study. In the study, patients in the total population were treated with therapy according to doctor's instructions, selecting pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine. Patients for whom treatment with gemcitabine was selected in the EMPOWER-Cervical 1 study prior to randomisation are not included in the relevant sub-population for the benefit assessment. The pharmaceutical company justifies the exclusion of the patients who were treated with gemcitabine with the comparator therapy originally determined in the consultation by the G-BA. Gemcitabine was not included in the comparators named by the G-BA – nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan and pembrolizumab (for patients with PD-L1 positive metastatic cervical cancer). The pharmaceutical company names another reason for the exclusion of gemcitabine with the comparator therapy for the procedure on pembrolizumab in combination with chemotherapy with or without bevacizumab in the indication of metastatic cervical cancer identified by the G-BA by resolution of 2 February 2023. In this resolution, when determining the appropriate comparator therapy for patients with persistent, recurrent or metastatic cervical cancer after first-line chemotherapy, who are eligible for further antineoplastic therapy, the G-BA also determines a therapy with the comparators nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan and pembrolizumab (for patients with PD-L1 positive metastatic cervical cancer) according to doctor's instructions. When preparing the dossier and in its written statement, the

pharmaceutical company assumed that the appropriate comparator therapy from the consultation or the pembrolizumab resolution of 2 February 2023 would be relevant again according to its opinion with the entry into force of the ALBVVG.

The sub-population presented includes 196 patients in the intervention arm and 183 patients in the chemotherapy arm (pemetrexed: n = 111; topotecan: n = 21; irinotecan: n = 19; vinorelbine: n = 32). This sub-population of patients in the EMPOWER-Cervical 1 study (excluding patients treated with gemcitabine) was evaluated for the present benefit assessment.

Limitation of the study; pretreatment with bevacizumab

According to the S3 guideline, patients with recurrent or metastatic cervical cancer should receive first-line treatment with cisplatin and paclitaxel or cisplatin with topotecan, each in combination with bevacizumab. In the EMPOWER-Cervical 1 study, about 55% of the patients in the sub-population presented did not receive prior treatment with bevacizumab. The reasons for this were the classification of patients as unsuitable for therapy with bevacizumab due to contraindications such as an unacceptable risk of fistula formation, poorly controlled hypertension, low-risk disease according to the Moore criteria, as well as the patient's refusal of therapy with bevacizumab. For the majority of patients, there was no access to therapy with bevacizumab for logistical reasons (e.g. no availability or no insurance cover). Thus, a total of 225 (37.0%) of all enrolled patients did not have access to therapy with bevacizumab for logistical reasons. Data for the sub-population submitted by the pharmaceutical company in the dossier are not available, but relevant difference in the percentage between the sub-population and the total population is not assumed. Overall, a relevant percentage of the enrolled patients were not pretreated according to the currently valid recommendations. This is a limitation of the EMPOWER-Cervical 1 study; the transferability of the results to the German healthcare context is therefore limited. However, these uncertainties are not rated so high as to justify a downgrading of the reliability of data of the overall assessment.

Implementation of the appropriate comparator therapy:

The "therapy according to doctor's instructions, selecting pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine" carried out as comparator therapy in the EMPOWER-Cervical 1 study comprises several treatment options that are also included in the appropriate comparator therapy determined by the G-BA in the context of therapy according to doctor's instructions. The only difference is the treatment with gemcitabine, which does not correspond to the appropriate comparator therapy determined by the G-BA. The therapy according to doctor's instructions carried out in the study is in line with the requirement that the study doctor should have a choice of several therapy options (multicomparator study).

The evaluations submitted by the pharmaceutical company on the sub-population which excluded patients for whom treatment with gemcitabine was selected prior to randomisation correspond to the appropriate comparator therapy. With reference to this sub-population, the comparator therapy of the EMPOWER-Cervical 1 study corresponds to an adequate implementation of the appropriate comparator therapy. The evaluations of the relevant sub-population are used as a basis for the assessment.

Extent and probability of the additional benefit

a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy

Mortality

Overall survival

The overall survival is defined in the EMPOWER-Cervical 1 study as the time from randomisation to death from any cause. For the endpoint of overall survival, there is a statistically significant difference between the treatment groups in favour of cemiplimab compared to a therapy according to doctor's instructions, selecting monotherapy with nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan and pembrolizumab (for patients with PD-L1 positive metastatic cervical cancer) (hereafter: chemotherapy).

The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

Morbidity

Progression-free survival (PFS)

PFS is operationalised in the Empower-Cervical 1 study as the time from randomisation to the first documentation of disease progression or death from any cause, whichever occurs first. The occurrence of disease progression was assessed using RECIST criteria (version 1.1).

For the PFS, there is a statistically significant difference between the treatment groups to the advantage of cemiplimab.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already assessed as an independent endpoint in the present study via the endpoint "overall survival". The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST version 1.1 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 additional benefit remains unaffected.

Symptomatology (assessed using EORTC QLQ-C30)

Symptomatology of the patients is assessed in the EMPOWER-Cervical 1 study using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30. In the dossier for the benefit assessment, the pharmaceutical company submitted responder analyses for this endpoint for the time to first deterioration by ≥ 10 points compared to baseline (scale range 0 to 100). However, there is uncertainty as to whether follow-up visits were included in the analyses.

For the endpoints of pain, nausea and vomiting as well as loss of appetite, there is a statistically significant difference respectively to the advantage of cemiplimab compared to chemotherapy.

Quality of life

Health-related quality of life is assessed in the EMPOWER-Cervical 1 study using the EORTC QLQ-C30 questionnaire. For the benefit assessment, the pharmaceutical company submitted responder analyses for this endpoint for the time to first deterioration by ≥ 10 points compared to baseline (scale range 0 to 100). However, there is uncertainty as to whether follow-up visits were included in the analyses.

For the endpoints of physical functioning, role functioning and social functioning, there was a statistically significant difference in favour of cemiplimab compared to the control arm.

Side effects

Serious AEs (SAEs)

For the endpoint of SAEs, there is no statistically significant difference between the treatment arms.

Severe AEs (CTCAE grade ≥ 3)

For the endpoint of severe AEs (CTCAE grade ≥ 3), there is a statistically significant difference to the advantage of cemiplimab compared to chemotherapy.

Therapy discontinuations due to AEs

For the endpoint of therapy discontinuations due to AEs, there is no statistically significant difference between the intervention and control arms.

Specific AEs

Immune-mediated SAEs and immune-mediated severe AEs (CTCAE grade ≥ 3)

No data were presented for the endpoint of immune-mediated SAEs. No suitable data are available for the endpoint of immune-mediated severe AEs (CTCAE grade ≥ 3).

Other specific AEs

For the other specific AEs of nausea (PT, AE) and blood and lymphatic system disorders (SOC, SAE) , there was a statistically significant difference to the advantage of cemiplimab compared to chemotherapy. For the endpoint of hepatobiliary disorders (SOC, severe AE [CTCAE grade ≥ 3]), there is a statistically significant difference to the disadvantage of cemiplimab compared to chemotherapy.

In the overall assessment of the results on side effects, an advantage can be determined overall for cemiplimab compared to chemotherapy.

Overall assessment

For the benefit assessment of cemiplimab, results from the EMPOWER-Cervical 1 study on the endpoint categories of mortality, morbidity, quality of life and side effects are available for cemiplimab in comparison with a therapy according to doctor's instructions consisting of the active ingredients pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine (hereafter: chemotherapy). For the benefit assessment, the evaluations submitted by the pharmaceutical company on a relevant sub-population (excluding patients treated with gemcitabine) are used.

For the endpoint of overall survival, there is a statistically significant difference between the treatment groups in favour of cemiplimab compared to chemotherapy. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

Symptomatology was assessed in the EMPOWER-Cervical 1 study using the symptom scales of the EORTC QLQ-C30 questionnaire.

For the endpoints of pain, nausea and vomiting as well as loss of appetite, there is a statistically significant difference respectively to the advantage of cemiplimab compared to chemotherapy.

With regard to the endpoint category of health-related quality of life (assessed using the EORTC QLQ-C30 questionnaire), there is a statistically significant difference in favour of cemiplimab compared to the control arm for each of the endpoints of physical functioning, role functioning and social functioning.

For the endpoint category of side effects, an advantage of cemiplimab compared to chemotherapy can be found overall based on a statistically significant reduction in severe AEs (CTCAE grade ≥ 3) and predominant advantages in specific AEs.

In the overall assessment, the G-BA identified a considerable additional benefit of cemiplimab compared to a therapy according to doctor's instructions, selecting a monotherapy with nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan and pembrolizumab (for patients with PD-L1 positive metastatic cervical cancer) for patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy and who are eligible for further antineoplastic therapy.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the open-label, randomised, multicentre controlled EMPOWER-Cervical 1 study.

Overall, the risk of bias at the study level is rated as low.

The endpoint-specific risk of bias is rated as high for the results of all patient-relevant endpoints, except overall survival.

The risk of bias in the results for the patient-reported endpoints of symptomatology and health-related quality of life (assessed with the EORTC QLQ-C30 questionnaire) is rated as high due to the lack of blinding in the subjective endpoint assessment. Results on non-serious and non-severe specific AEs show a high risk of bias due to the lack of blinding. The results of the endpoint of therapy discontinuation due to AEs have a high risk of bias due to the lack of blinding in the subjective endpoint assessment.

According to the S3 guideline, patients with recurrent or metastatic cervical cancer should receive first-line treatment with cisplatin and paclitaxel or cisplatin with topotecan, each in combination with bevacizumab. However, in the EMPOWER-Cervical 1 study, about 55% of the patients in the sub-population presented did not receive prior treatment with bevacizumab. Therefore, uncertainty results regarding the transferability of the study results to the German healthcare context. However, this uncertainty is not rated so high as to justify a downgrading of the reliability of data.

Overall, the available data basis is subject to uncertainties. However, these uncertainties are not rated 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 for the additional benefit determined is classified in the category "indication".

b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy

An additional benefit is not proven.

Justification:

No data for an assessment of the additional benefit of cemiplimab in this patient group or in comparison to best supportive care were submitted with the dossier by the pharmaceutical company. Thus, an additional benefit for patients who are ineligible for further antineoplastic therapy is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient cemiplimab. The therapeutic indication assessed here is as follows:

"LIBTAYO as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy."

In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy

b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy

Patient group a)

The G-BA determined the appropriate comparator therapy to be a therapy according to doctor's instructions, selecting a monotherapy with nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan or pembrolizumab (for patients with PD-L1 positive cervical cancer).

For the benefit assessment, the pharmaceutical company submits the results of a relevant sub-population (excluding the patients treated with gemcitabine) of the EMPOWER-Cervical 1 study, in which cemiplimab is compared to a therapy according to doctor's instructions consisting of the active ingredients pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine (hereafter: chemotherapy). This comparator therapy corresponds to the appropriate comparator therapy.

For the endpoint of overall survival, there is an advantage of cemiplimab compared to chemotherapy, which is assessed as a significant improvement.

In the endpoint categories of morbidity and health-related quality of life, there are advantages of cemiplimab compared to chemotherapy.

For side effects, there is an advantage of cemiplimab in the endpoint of severe AEs (CTCAE grade ≥ 3) as well as advantages in specific AEs.

As a result, the G-BA identified an indication of a considerable additional benefit compared to the appropriate comparator therapy - therapy according to doctor's instructions, selecting a monotherapy with nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan or pembrolizumab (for patients with PD-L1 positive cervical cancer).

Patient group b)

For the groups of patients who are ineligible for further antineoplastic therapy, the G-BA determined best supportive care as an appropriate comparator therapy.

For this patient group, no data are available for the assessment of the additional benefit. An additional benefit is not proven.

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

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

The resolution is based on the information from IQWiG's dossier assessment, as the information provided by the pharmaceutical company is subject to uncertainties.

The 5-year prevalence used as a basis by the pharmaceutical company leads to uncertainties in the derivation of patient numbers. Methodologically, the incidence used by IQWiG would be a more appropriate baseline. It should be noted that the number of patients in IQWiG's calculation is also subject to uncertainty.

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 Libtayo (active ingredient: cemiplimab) at the following publicly accessible link (last access: 10 October 2023):

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

Therapy with cemiplimab 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 cervical cancer.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card).

The training material contains, in particular, information and warnings about immune-mediated side effects as well as infusion-related reactions.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE (last revised: 1 October 2023).

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 varies from patient to patient 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.

As it is not always possible to achieve the exact target dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

The treatment costs for best supportive care are different from patient to patient. Because best supportive care has been determined as an appropriate comparator therapy, this 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.

For the presentation of the costs, one year is assumed for all medicinal products.

The information on dosages refers to applications in women, as cervical cancer occurs only in women. The average body measurements of adult females were applied for dosages, depending on body weight (BW) or body surface area (BSA) (average body height: 1.66 m; average body weight: 68.7 kg). This results in a body surface area of 1.76 m² (calculated according to Du Bois 1916).[11]

There is no marketing authorisation for nab-paclitaxel, pembrolizumb, pemetrexed, vinorelbine, ifosfamide, irinotecan and topotecan in patients with recurrent or metastatic cervical cancer. For the cost calculation in the context of the off-label use of these active ingredients for the treatment of recurrent or metastatic cervical cancer, the G-BA uses the corresponding information on dosage in the S3 guideline[12] as a basis. For ifosfamide, the product information was used as the basis for calculation. The dosage of ifosfamide (1.2 g - 2.4 g/m^2 BSA on day 1-5 of a 21-day or 28-day cycle) was based on the most common dosage for monotherapy. The dosages of irinotecan (1 x 125 mg/m^2 BSA every 7 days), nab-paclitaxel (125 mg/m^2 BSA on day 1 + 8 + 15 of a 21-day cycle), pembrolizumab (200 mg every 21 days), pemetrexed (500 mg/m^2 BSA every 21 days) topotecan (1 x 1.5 mg/m^2 BSA on day 1 - 5 per 21-day cycle) and vinorelbine (30 mg/m^2 BSA on day 1 + 8 of a 21-day cycle) correspond to the information in the S3 guideline on cervical cancer[12].

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

[12] Guideline programme on oncology, S3 guideline Diagnostics, therapy and after-care of patients with cervical cancer, long version 2.2 - March 2022.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Patient population a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy				
Medicinal product to be assessed				
Cemiplimab	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Therapy according to doctor's instructions				
Ifosfamide + mesna				
Ifosfamide	1 x on day 1 - 5 of a 21 or 28-day cycle	13.0 or 17.4	5	65.0 or 87.0
Mesna	3 x on day 1 - 5 of a 21 or 28-day cycle	13.0 or 17.4	5	65.0 or 87.0
Irinotecan	1 x per 7-day cycle	52.1	1	52.1
nab-paclitaxel	1 x on day 1 + 8 + 15 of a 21-day cycle	17.4	3	52.2
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Topotecan	1 x on day 1-5 per 21-day cycle	17.4	5	87.0
Vinorelbine	1 x on day 1 and 8 per 21-day cycle	17.4	2	34.8
Patient population b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy				
Medicinal product to be assessed				
Cemiplimab	1 x per 21-day cycle	17.4	1	17.4
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treat-ment days/ patient/ year	Annual average consumption by potency
Patient population a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy					
Medicinal product to be assessed					
Cemiplimab	350 mg	350 mg	1 x 350 mg	17.4	17.4 x 350 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions					
Ifosfamide + mesna					
Ifosfamide	1,200 mg/m² – 2,400 mg/m² = 2,112 mg – 4,224 mg	2,112 mg	1 x 1,000 mg + 1 x 2,000 mg	65.0 – 87.0	65.0 - 87.0 x 1,000 mg + 65.0 - 87.0 x 2000 mg
		4,224 mg	1 x 5,000 mg		65.0 - 87.0 x 5,000 mg
Mesna (IV)	240 mg/m² – 480 mg/m² = 422.4 mg – 844.8 mg	3 x 422.4 mg	3 x 2 x 400 mg	65.0 – 87.0	390 – 522 x 400 mg
		3 x 844.8 mg	3 x 3 x 400 mg		585 – 783 x 400 mg
Irinotecan	125 mg/m² = 220 mg	220 mg	1 x 300 mg	52.1	52.1 x 300 mg
nab-paclitaxel	125 mg/m² = 220 mg	220 mg	3 x 100 mg	52.2	156.6 x 100 mg
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
Pemetrexed	500 mg/m² = 880 mg	880 mg	2 x 500 mg	17.4	34.8 x 500 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treat-ment days/ patient/ year	Annual average consumption by potency
Topotecan	1.5 mg/m² = 2.64 mg	2.64 mg	1 x 3 mg	87	87 x 3 mg
Vinorelbine	30 mg/m² = 52.8 mg	52.8 mg	1 x 50 mg 1 x 10 mg	34.8	34.8 x 50 mg 34.8 x 10 mg
Patient population b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy					
Medicinal product to be assessed					
Cemiplimab	350 mg	350 mg	1 x 350 mg	17.4	17.4 x 350 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				

Costs:

Costs of the medicinal products:

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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Designation of the therapy	Packaging size	Costs (pharma-cy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Patient population a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy					
Medicinal product to be assessed					
Cemiplimab 350 mg	1 CIS	€ 5,148.68	€ 2.00	€ 498.43	€ 4,648.25
Appropriate comparator therapy					
Ifosfamide 1 g	1 INF	€ 49.88	€ 2.00	€ 1.83	€ 46.05
Ifosfamide 2 g	1 INF	€ 80.24	€ 2.00	€ 3.27	€ 74.97
Ifosfamide 5 g	1 CIS	€ 177.77	€ 2.00	€ 7.90	€ 167.87
Mesna 400 mg	50 AMP	€ 148.19	€ 2.00	€ 17.33	€ 128.86
Irinotecan 300 mg	1 CIS	€ 573.94	€ 2.00	€ 71.20	€ 500.74
nab-paclitaxel 100 mg	1 PIS	€ 429.36	€ 2.00	€ 19.84	€ 407.52
Pembrolizumab 100 mg	1 CIS	€ 2,974.82	€ 2.00	€ 285.60	€ 2,687.22
Pemetrexed 500 mg	1 PCI	€ 517.04	€ 2.00	€ 24.00	€ 491.04
Topotecan 3 mg	1 CIS	€ 236.46	€ 2.00	€ 21.37	€ 213.09
Vinorelbine 50 mg	10 CIS	€ 1,424.56	€ 2.00	€ 67.07	€ 1,355.49
Vinorelbine 10 mg	10 CIS	€ 294.01	€ 2.00	€ 13.42	€ 278.59
Patient population b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy					
Medicinal product to be assessed					
Cemiplimab 350 mg	1 CIS	€ 5,148.68	€ 2.00	€ 498.43	€ 4,648.25
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Abbreviations: AMP = ampoules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; INF = infusion solution; PCI = powder for a concentrate for the preparation of an infusion solution; PIS = powder for the preparation of an infusion suspension					

LAUER-TAXE® last revised: 1 October 2023

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.

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
Appropriate comparator therapy							
Pemetrexed							
17.4 cycles							
Dexamethasone [13] 2 x 4 mg	100 x 4 mg TAB	€ 79.54	€ 2.00	€ 5.40	€ 72.14	52.2	€ 72.14
	20 x 4 mg TAB	€ 24.61	€ 2.00	€ 1.05	€ 21.56		€ 4.74
Folic acid [14] 350 – 1.000 µg/day	30 x 400 µg TAB	€ 3.10	€ 0.00	€ 0.00	€ 3.10	365	€ 37.72 - € 75.43
Vitamin B12[13] 1,000 µg/day, every 3 cycles	10 x 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.32	€ 6.71	5.8	€ 3.89

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 € 100 per ready-to-use preparation, and

[13] Fixed reimbursement rate

[14] The cost calculation for folic acid is based on the single dose of 400 µg of the non-divisible tablets available for cost calculation related to a dose range of 400 - 800 µg per day, even if a dose range of 350 - 1,000 µg is given in the product information.

for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is authorised exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called undetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

<u>Concomitant active ingredient:</u>

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the

combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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 12 October 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 23 May 2023.

On 19 April 2023, the pharmaceutical company submitted a dossier for the benefit assessment of cemiplimab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 2.

By letter dated 24 April 2023 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 cemiplimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 July 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2023. The deadline for submitting statements was 22 August 2023.

The oral hearing was held on 11 September 2023.

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 10 October 2023, and the proposed resolution was approved.

At its session on 19 October 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 October 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	23 May 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	6 September 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 September 2023	Conduct of the oral hearing,
Working group Section 35a	20 September 2023 4 October 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	10 October 2023	Concluding discussion of the draft resolution
Plenum	19 October 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 19 October 2023

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

Prof. Hecken