Gemeinsamer Bundesausschuss

Justification

to 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 Tisotumab vedotin (cervical cancer, pretreated)

of 19 February 2026

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all 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 studies the pharmaceutical company have 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,
7. number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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 decide 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient tisotumab vedotin on 1 September 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. Pursuant to Section 4, paragraph 3, No. 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, No. 1 Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 28 August 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 December 2025 on the G-BA website at (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 tisotumab vedotin 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 have 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 tisotumab vedotin.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have made 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 Tisotumab vedotin (Tivdak) in accordance with the product information

Tivdak as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.

Therapeutic indication of the resolution (resolution of 19.02.2026):

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 with disease progression on or after platinum-based first-line chemotherapy, who have not been pretreated with a PD-(L)1 antibody and who are eligible for further systemic, antineoplastic standard therapy

Appropriate comparator therapy for tisotumab vedotin as monotherapy:

- Cemiplimab

b) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after
   - platinum-free first-line chemotherapy without a PD-(L)1 antibody,
   - first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody,
   - sequential therapy with platinum-based chemotherapy and a PD-(L)1 antibody

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

who are eligible for further systemic, antineoplastic standard therapy

Appropriate comparator therapy for tisotumab vedotin as monotherapy:

Individualised therapy with selection of monotherapy with:

- Nab-paclitaxel
- Vinorelbine
- Ifosfamide
- Topotecan
- Pemetrexed
- Irinotecan
- Pembrolizumab (only patients with PD-L1-positive cervical cancer [CPS score ≥1] who have not been pretreated with a PD-(L)1 antibody are eligible)

c) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after prior systemic therapy who are ineligible for further systemic, antineoplastic standard therapy

Appropriate comparator therapy for tisotumab vedotin as monotherapy:

- Best supportive care

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 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 they determine 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.

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

On 1. In addition to tisotumab vedotin, the active ingredients bleomycin, carboplatin, cemiplimab, cisplatin and mitomycin as well as the combination therapies of 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. A non-medicinal treatment is not considered in the present therapeutic indication. It is assumed that surgery and/or radiotherapy with a curative objective are not (no longer) an option at the time of the treatment decision and that palliative treatment is given. 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. In the present therapeutic indication, the following resolutions on the benefit assessment of medicinal products according to Section 35a SGBV are available:

- Cemiplimab: resolution of 19 October 2023
- 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 indication according to Section 35a paragraph 7 SGB

V (see “Information on Appropriate Comparator Therapy”). There is a joint written statement from the German Society of Gynaecology and Obstetrics (DGGG), German Society for Haematology and Medical Oncology (DGHO) and the North-East German Society for Gynaecological Oncology (NOGGO) (hereinafter: the scientific-medical societies).

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.

The approved therapeutic indication presumes "disease progression on or after systemic therapy". Prior systemic therapy in the present therapeutic indication comprises chemotherapy that may be combined with or without bevacizumab and/or with or without a PD-(L)1 antibody in accordance with the marketing authorisation of the chemotherapeutic agents or combinations of active ingredients. The progression of patients can thus occur on or after systemic combination chemotherapy or on platinum-based chemotherapy (sequentially or in combination in 1 – 2 previous lines of therapy).

For patients with cervical cancer, treatment with a PD-(L)1 antibody (either as combination therapy or as monotherapy) is a therapy option that can be used both in first-line therapy and after prior therapy. The present therapeutic indication covers patients who may already have been pretreated with a PD-(L)1 antibody (either as combination therapy or as monotherapy). With regard to retreatment with a PD-(L)1 antibody, the scientific-medical societies state in their written opinion that it is currently unclear whether immunotherapy is also effective to the same extent after prior therapy with an immune checkpoint inhibitor. Current guidelines make the therapy recommendation depending on prior PD-(L)1 antibody therapy.

Furthermore, the treatment decision depends on the suitability of patients for further antineoplastic therapy.

Overall, the treatment decision is made in the present treatment setting, depending on the (immune checkpoint inhibitor) prior therapy and the suitability of the patients for further antineoplastic therapy. The G-BA therefore consider it appropriate to distinguish between three patient groups when determining the appropriate comparator therapy:

a) <u>Adult patients with recurrent or metastatic cervical cancer with disease progression on or after platinum-based first-line chemotherapy, who have not been pretreated with a PD-(L)1 antibody and who are eligible for further systemic, antineoplastic standard therapy</u>

The current ESGO/ESTRO/ESP guideline recommends[2] the PD-1 antibody cemiplimab for patients with disease progression after platinum-based first-line chemotherapy without a PD-(L)1 antibody. The active ingredient cemiplimab is not yet included in the

[2] Cibula et al., 2023. ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer – Update 2023. Int J Gynecol Cancer. 2023 May 1;33(5):649-666

S3 guideline[3] due to the timeliness of the marketing authorisation of cemiplimab. No recommendations for this patient group can be derived from the available evidence for the active ingredient pembrolizumab in combination with chemotherapy with or without bevacizumab, with pembrolizumab also having been formally approved for the present treatment setting. Pembrolizumab in combination with chemotherapy with or without bevacizumab is therefore not determined as the appropriate comparator therapy.

In their written statement, the scientific-medical societies explain that immunotherapy with cemiplimab was the previous treatment standard for patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.

The marketing authorisation of cemiplimab explicitly presumes prior therapy with platinum-based chemotherapy. In the corresponding benefit assessment, an indication of a considerable additional benefit of cemiplimab was identified for adult patients with recurrent or metastatic cervical cancer with disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy (resolution of 19 October 2023).

In the overall assessment of the available evidence, the G-BA determined cemiplimab as the appropriate comparator therapy.

b) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after
   - platinum-free first-line chemotherapy without a PD-(L)1 antibody,
   - first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody,
   - sequential therapy with platinum-based chemotherapy and a PD-(L)1 antibody

   who are eligible for further systemic, antineoplastic standard therapy

According to the S3 guideline, mono-chemotherapy is generally recommended in the present treatment setting for eligible patients who wish to undergo treatment. The ESGO/ESTRO/ESP guideline also mentions the possibility of chemotherapy. In this regard, the active ingredients nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed and irinotecan are mentioned as possible therapy options in the S3 guideline. For patients with PD-L1 positive metastatic cervical cancer, pembrolizumab (monotherapy) is also mentioned as a possible therapy option in the guidelines. In the S3 guideline, a phase II study is referenced for each of the aforementioned therapy

[3] Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (German Society for Gynaecology and Obstetrics) (DGGG) 2022. S3 guideline on diagnostics and therapy and after-care for patients with cervical cancer. AWMF online. S3 guideline on cervical cancer - long version (awmf.org)

options.[4,5,6,7,8,9,10] These active ingredients are not approved in the present therapeutic indication and are used off-label.

As described above, it should be noted that cemiplimab is only approved for use after platinum-based chemotherapy. In addition, the ESGO/ESTRO/ESP guideline restricts the use of cemiplimab to patients who have not previously received immunotherapy. Furthermore, pembrolizumab in combination with chemotherapy with or without bevacizumab is approved in the present treatment setting. However, the guidelines and written statements from the scientific-medical societies do not contain any recommendation for the present treatment setting and patient population. 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 and the written statement of the scientific-medical societies. Cemiplimab and pembrolizumab in combination with chemotherapy with or without bevacizumab are therefore not considered as the appropriate comparator therapy.

According to the scientific-medical societies, mono-chemotherapy is currently the recommended therapy in the reality of care for a selected patient population in case of progression after systemic first-line therapy, with reference being made to the mono-chemotherapies specified in the S3 guideline.

In this regard, the S3 guideline and the scientific-medical societies state that, for the present treatment setting, there are currently no treatment studies that show an improvement in overall survival for a therapy option of the above-mentioned patients compared to best supportive care. The treatment objective is disease control and symptom relief. According to the scientific-medical societies, best supportive care, which also includes the use of effective cytostatic agents to alleviate symptoms, is in line with the recommendations. According to the S3 guideline and the written statement of the scientific-medical societies, monotherapy with the checkpoint inhibitor pembrolizumab is another option for patients with PD-L1 positive metastatic cervical cancer.

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

---

[4] Alberts, D.S., et al., Phase II trial of nab-paclitaxel in the treatment of recurrent or persistent advanced cervix cancer: A gynaecologic oncology group study. Gynaecol 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 Gynaecologic Oncology Group study. Gynaecol Oncol, 2004. 92(2): p. 639-43

[6] Sutton, G.P., et al., A phase II Gynaecologic Oncology Group trial of ifosfamide and mesna in advanced or recurrent adenocarcinoma of the endometrium. Gynaecol 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 Gynaecologic Oncology Group. Gynaecol 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 Gynaecologic 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

In the overall assessment, the G-BA determined the appropriate comparator therapy for the present treatment setting to be an individualised therapy with the selection of a monotherapy with nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan and pembrolizumab (for patients with PD-L1 positive cervical cancer [CPS score ≥ 1]).

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 options pembrolizumab in combination with chemotherapy with or without bevacizumab as well as monotherapy with cemiplimab are not considered as an appropriate comparator therapy for the aforementioned reasons. The other approved active ingredients listed under 1. do not comply with the guideline recommendations for the present indication and do not correspond to the statements made by clinicians regarding the therapy standard in the reality of care.

The S3 guideline references a phase II study for each of the aforementioned therapy options[4,5,6,7,8,9,10]. Compared to the monotherapies and combination therapies approved for use in the therapeutic indication, monotherapies with nab-paclitaxel, vinorelbine, pemetrexed, irinotecan, ifosfamide, topotecan or pembrolizumab in off-label use are thus considered the therapy standard for patient population b) according to the generally recognised state of medical knowledge, in accordance with Section 6, paragraph 2, sentence 3, no. 2 AM-NutzenV, and shall generally be preferred. 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.

c) <u>Adult patients with recurrent or metastatic cervical cancer with disease progression on or after prior systemic therapy who are ineligible for further systemic, antineoplastic standard therapy</u>

The present therapeutic indication also includes patients who are ineligible for further systemic antineoplastic therapy in accordance with the current treatment standard (see above explanations).

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 in the benefit assessment procedure for cemiplimab (resolution of 19.10.2023), this patient group is considered to be of relevant significance in the present therapeutic indication.

For the group of patients who are ineligible for further systemic, antineoplastic standard therapy, best supportive care (BSC) is determined as the appropriate comparator therapy. Best supportive care (BSC) is defined as the therapy that provides the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

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

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO.

Change in the appropriate comparator therapy (editorial):

Compared to the originally determined appropriate comparator therapy, the designations of patient groups a), b) and c) have been changed in the present resolution. The characteristic "who are (not) eligible for further antineoplastic therapy" is replaced in all patient groups by "who are (not) eligible for further systemic, antineoplastic standard therapy". This is merely a clarifying editorial change to the patient group designations. This does not result in any change in content and the present assessment of tisotumab vedotin remains unaffected.

2.1.3 Extent and probability of the additional benefit

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

a) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after platinum-based first-line chemotherapy, who have not been pretreated with a PD-(L)1 antibody and who are eligible for further systemic, antineoplastic standard therapy

An additional benefit is not proven.

b) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after

- platinum-free first-line chemotherapy without a PD-(L)1 antibody,
- first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody,
- sequential therapy with platinum-based chemotherapy and a PD-(L)1 antibody

who are eligible for further systemic, antineoplastic standard therapy

An additional benefit is not proven.

c) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after prior systemic therapy who are ineligible for further systemic, antineoplastic standard therapy

An additional benefit is not proven.

Justification:

a) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after platinum-based first-line chemotherapy, who have not been pretreated with a PD-(L)1 antibody and who are eligible for further systemic, antineoplastic standard therapy

Justification:

With the dossier, the pharmaceutical company did not submit any data for patient group a for an assessment of the additional benefit of trastuzumab vedotin compared to the appropriate comparator therapy. Therefore, an additional benefit is not proven.

b) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after

- platinum-free first-line chemotherapy without a PD-(L)1 antibody,
- first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody,
- sequential therapy with platinum-based chemotherapy and a PD-(L)1 antibody

who are eligible for further systemic, antineoplastic standard therapy

In the benefit assessment dossier, the pharmaceutical company presented the results from the ongoing innovaTV 301 approval study on tisotumab vedotin. This is an open-label, randomised phase III study comparing tisotumab vedotin with chemotherapy selected by the principal investigator. The therapy options available were monotherapies with topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed.

A total of 502 patients with recurrent or metastatic cervical cancer of any histology with disease progression on or after platinum-free or platinum-based chemotherapy with or without a PD-(L)1 antibody were enrolled in the study. The patients could have received these systemic therapies in 1 or 2 lines of therapy. Patients were randomised in a 1:1 ratio, with 253 patients having been assigned to the intervention arm and 249 patients to the chemotherapy arm.

The study ongoing since 2021 is being conducted in 25 study sites in Asia, Europe as well as North America and South America.

In the dossier, the pharmaceutical company presented data on the primary and final data cut-off from 24 July 2023.

On the data cut-off

In the benefit assessment, the IQWiG criticises the fact that the pharmaceutical company presented the 1st data cut-off from 24 July 2023 (prespecified interim analysis, planned after 252 deaths in the total population), since a further 2nd prespecified data cut-off (final analysis of overall survival planned after 336 deaths in the total population) was planned and an additional data cut-off from 16 January 2024 was made available to the EMA. Although the data cut-off from 16 January 2024 was made available to the EMA, this had no influence on the marketing authorisation of the medicinal product according to the pharmaceutical company's statement and was classified as irrelevant in accordance with the guidelines for dossier preparation. The fact that the pharmaceutical company did not submit any data for the data cut-off from 16 January 2024 has no consequences for the present benefit assessment of tisotumab vedotin, as the pharmaceutical company did not submit any suitable data in any case (see next section).

Relevant sub-population and implementation of the appropriate comparator therapy:

The pharmaceutical company supportively presented the results for the total population of the innovaTV 301 study in the dossier for patient group b and justifies this with a small population size after cutting off the patient population for the benefit assessment.

The relevant sub-population of patient group b for the benefit assessment comprises, in accordance with the criteria defined by the G-BA, patients who have received prior treatment with platinum-free chemotherapy without a PD-(L)1 antibody, first-line therapy consisting of chemotherapy and a PD-(L)1 antibody, or sequential platinum-based chemotherapy and a PD-(L)1 antibody. For the implementation of the appropriate comparator therapy, patients were able to receive a therapy option as part of individualised therapy from the comparators

specified by the G-BA: nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan and pembrolizumab (for patients with PD-L1-positive metastatic cervical cancer).

The number of patients who met the criteria for pretreatment in the innovaTV 301 study and who received the therapy options vinorelbine, topotecan, pemetrexed and irinotecan in accordance with the appropriate comparator therapy was 63. 32 patients thereof were assigned to the intervention arm and 31 patients to the control arm. The comparators specified by the G-BA did not include gemcitabine - the therapy option used in the study. Furthermore, the therapy options of nab-paclitaxel, ifosfamide and pembrolizumab specified by the G-BA as part of individualised therapy were not used in the innovaTV 301 study.

The determination of the appropriate comparator therapy results in patient groups that differ depending on the previous therapy. For patient group b, the pharmaceutical company only presented results for the total population of the innovaTV 301 study. They justify presenting data on the total population instead of the cut-off for the relevant sub-population by arguing that the analysis population is unsuitable due to the small population size and the resulting uncertainties regarding effect estimates and the limited reliability of the conclusions drawn from it. The presentation of data on the total population is considered inappropriate.

The data on the total population are unsuitable for the assessment of the additional benefit for patient group b, as 72% of the patients with progression on or after first-line platinum-based chemotherapy, who were not pretreated with a PD-(L)1 antibody, were enrolled in the innovaTV 301 study. These patients are assigned to patient group a in the benefit assessment. The appropriate comparator therapy for patient group a – cemiplimab – was not a therapy option in the innovaTV 301 study.

For patient group b, no data were presented for the relevant sub-population that corresponded to the pretreatment and met the criteria for the implementation of the appropriate comparator therapy. Thus, no suitable data versus the appropriate comparator therapy are available.

In the overall assessment, there are no suitable data for patient group b for the assessment of the additional benefit of tisotumab vedotin. An additional benefit of tisotumab vedotin is therefore not proven for patient group b.

c) <u>Adult patients with recurrent or metastatic cervical cancer with disease progression on or after prior systemic therapy who are ineligible for further systemic, antineoplastic standard therapy</u>

Justification:

With the dossier, the pharmaceutical company did not submit any data for patient group c for an assessment of the additional benefit of trastuzumab vedotin compared to the appropriate comparator therapy. Therefore, an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Tivdak with the active ingredient tisotumab vedotin.

The therapeutic indication assessed here is as follows:

"Tivdak as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy."

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

a) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after platinum-based first-line chemotherapy, who have not been pretreated with a PD-(L)1 antibody and who are eligible for further systemic, antineoplastic standard therapy

The appropriate comparator therapy was determined as follows by the G-BA: Cemiplimab.

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

b) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after

- platinum-free first-line chemotherapy without a PD-(L)1 antibody,
- first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody,
- sequential therapy with platinum-based chemotherapy and a PD-(L)1 antibody

who are eligible for further systemic, antineoplastic standard therapy

The appropriate comparator therapy was determined as follows by the G-BA: Individualised therapy with selection of nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan and pembrolizumab.

For patient group b, the pharmaceutical company presented the results for the total population of the innovaTV 301 study. The innovaTV 301 study is an open-label, randomised phase III study comparing tisotumab vedotin with chemotherapy with selection of topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed. However, the data on the total population are unsuitable for the assessment of the additional benefit for patient group b, as patients who were not pretreated with a PD-(L)1 antibody were mainly enrolled in the study. These patients are assigned to patient group a in the benefit assessment. For patient group b, no data were presented for the relevant sub-population that corresponded to the pretreatment and met the criteria for the implementation of the appropriate comparator therapy. Thus, no suitable data versus the appropriate comparator therapy are available. An additional benefit is therefore not proven.

c) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after prior systemic therapy who are ineligible for further systemic, antineoplastic standard therapy

For this patient group, no data are available for the assessment of the additional benefit. An additional benefit is therefore 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 the resolution on the benefit assessment of cemiplimab for the therapeutic indication "recurrent or metastatic cervical cancer with disease progression on or after platinum-based chemotherapy" (resolution of 19 October

2023). The restriction to patients who had received platinum-based chemotherapy as prior therapy was not applied when determining the number of patients in the cemiplimab procedure.

The patient number determined by the pharmaceutical company is subject to uncertainties, but is comparable - with regard to the lower limit - to the number of patients treated with the previous procedure of cemiplimab. There are uncertainties regarding the derivation of the upper limit by the pharmaceutical company, which concern the percentage values for the recurrence rate and the consideration of all patients who show disease progression after receiving systemic first-line therapy.

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of cemiplimab (resolution of 19 October 2023). A valid estimate of the number of female patients in the SHI target population is available here; this can be used despite continuing uncertainties.

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 Tivdak (active ingredient: tisotumab vedotin) at the following publicly accessible link (last access: 11 February 2026):

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

Therapy with tisotumab vedotin should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, who are experienced in the treatment of patients with cervical cancer, specialists in obstetrics and gynaecology, and other doctors from other specialist groups participating in the Oncology Agreement.

Prior to treatment with tisotumab vedotin and in the event of corresponding clinical indication, an eye examination should be carried out by an ophthalmologist. The patients' eyes must also be examined by the treating doctors prior to each infusion, including checking for normal eye movements. Prior to each infusion, patients must also be questioned and monitored by the treating doctors for evidence of disease or newly occurring or deteriorating eye symptoms and, if necessary, referred to an ophthalmologist as soon as possible. Patients must also be instructed to report any new or intensifying evidence of disease or eye symptoms to their treating doctor or specialist staff.

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 December 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

The annual treatment costs shown refer to the first year of treatment.

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

different 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 co-morbidities) 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 dosage strengths, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dosage strengths as well as the scalability of the respective dosage form.

For dosages depending on body weight (bw) or body surface area (BSA), the average body measurements of adult females from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.66 m, average body weight: 69.2 kg)[11]. This results in a body surface area of 1.77 m² (calculated according to Du Bois 1916).

a) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after platinum-based first-line chemotherapy, who have not been pretreated with a PD-(L)1 antibody and who are eligible for further systemic, antineoplastic standard therapy

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tisotumab vedotin	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Cemiplimab	1 x per 21-day cycle	17.4	1	17.4

[11] Federal health reporting. Average body measurements of the population (2021, women, 15 years and older), https://www.gbe-bund.de/

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tisotumab vedotin	2 mg/ kg BW	138.4 mg	4 x 40 mg	17.4	69.6 x 40 mg
Appropriate comparator therapy					
Cemiplimab	350 mg	350 mg	1 x 350 mg	17.4	17.4 x 350 mg

b) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after

- platinum-free first-line chemotherapy without a PD-(L)1 antibody,
- first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody,
- sequential therapy with platinum-based chemotherapy and a PD-(L)1 antibody

who are eligible for further systemic, antineoplastic standard therapy

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[2].

[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
Medicinal product to be assessed				
Tisotumab vedotin	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Individualised therapy with selection of monotherapy with ifosfamide, irinotecan, nab-paclitaxel, pemetrexed, pembrolizumab (only patients with PD-L1-positive cervical cancer [CPS score ≥ 1] who have not been pretreated with a PD-(L)1 antibody are eligible), topotecan, vinorelbine				
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
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

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tisotumab vedotin	2 mg/ kg BW	138.4 mg	4 x 40 mg	17.4	69.6 x 40 mg
Appropriate comparator therapy					
Individualised therapy with selection of monotherapy with ifosfamide, irinotecan, nab-paclitaxel, pemetrexed, pembrolizumab (only patients with PD-L1-positive cervical cancer [CPS score ≥ 1] who have not been pretreated with a PD-(L)1 antibody are eligible), topotecan, vinorelbine					
Ifosfamide	1,200 mg/m² – 2,400 mg/m²	2,124 mg	1 x 1,000 mg + 1 x 2,000 mg	65.0	65.0 x 1,000 mg + 65.0 x 2,000 mg – 65.0 x 5,000 mg
		–	–	or	or
		4,248 mg	1 x 5,000 mg	87.0	87.0 x 1,000 mg + 87.0 x 2,000 mg – 87.0 x 5,000 mg
Irinotecan	125 mg/m² BSA	221.3 mg	1 x 300 mg	52.1	52.1 x 300 mg
Nab-paclitaxel	125 mg/m² BSA	221.3 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 BSA	885 mg	2 x 500 mg	17.4	34.8 x 500 mg
Topotecan	1.5 mg/m² BSA	2.7 mg	1 x 3 mg	87.0	87.0 x 3 mg
Vinorelbine	30 mg/m² BSA	53.1 mg	1 x 50 mg + 1 x 10 mg	34.8	34.8 x 50 mg + 34.8 x 10 mg

c) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after prior systemic therapy who are ineligible for further systemic, antineoplastic standard therapy

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.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tisotumab vedotin	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	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tisotumab vedotin	2 mg/ kg BW	138.4 mg	4 x 40 mg	17.4	69.6 x 40 mg
Best supportive care		Different from patient to patient			
Appropriate comparator therapy					
Best supportive care					
Best supportive care		Different from patient to patient			

Costs:

Patient groups a) – c)

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 reference prices shown in the cost representation may not represent the cheapest available alternative.

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					
Tisotumab vedotin 40 mg	1 PCI	€ 2,289.66	€ 1.77	€ 127.47	€ 2,160.42
Appropriate comparator therapy					
Cemiplimab 350 mg	1 CIS	€ 4,321.44	€ 1.77	€ 243.51	€ 4,076.16
Ifosfamide 5,000 mg	1 CIS	€ 177.77	€ 1.77	€ 7.90	€ 168.10
Ifosfamide 2,000 mg	1 INF	€ 80.24	€ 1.77	€ 3.27	€ 75.20
Ifosfamide 1,000 mg	1 INF	€ 49.88	€ 1.77	€ 1.83	€ 46.28
Irinotecan 300 mg	1 CIS	€ 568.26	€ 1.77	€ 66.44	€ 500.05
Nab-paclitaxel 100 mg	1 PIS	€ 429.36	€ 1.77	€ 19.84	€ 407.75
Pembrolizumab 100 mg	2 CIS	€ 4,962.26	€ 1.77	€ 280.10	€ 4,680.39
Pemetrexed 500 mg	1 PCI	€ 567.62	€ 1.77	€ 26.40	€ 539.45
Topotecan 3 mg	1 CIS	€ 236.46	€ 1.77	€ 12.47	€ 222.22
Vinorelbine 50 mg	5 CIS	€ 152.64	€ 1.77	€ 6.71	€ 144.16
Vinorelbine 10 mg	1 CIS	€ 38.90	€ 1.77	€ 1.31	€ 35.82
Abbreviations: CIS = concentrate for the preparation of an infusion solution; INF = infusion solution; PIS = powder for the preparation of an infusion suspension; PCI = powder for a concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 December 2025

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.

The calculation of the additionally required SHI services is based on packs in distribution with the LAUER-TAXE® last revised on 15 September 2025 and fee structure items (FSI) - last revised in the 3rd quarter of 2025 of the uniform value scale (UVS 2025/Q3).

Ophthalmological examination

Due to the risk of possible ocular side effects, an ophthalmological examination is necessary prior to treatment with tisotumab vedotin. During treatment, the treating doctor must perform an eye examination prior to each infusion.

According to the product information for the medicinal product to be assessed, corticosteroid-containing, vasoconstrictive and moisturising eye drops are also used. For the latter, the costs are estimated by the example of a daily dosage of 3-5 drops per eye.

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
Medicinal product to be assessed							
Tisotumab vedotin; topical preservative-free corticosteroid-containing and vasoconstrictive eye drops, moisturising eye drops							
Dexamethasone 0.1%	50 egtts	€ 31.61	€ 1.77	€ 0.96	€ 28.88	87	€ 150.75
Brimonidine tartrate 0.2%	120 SDP	€ 91.75	€ 1.77	€ 4.45	€ 85.53	17.4	€ 12.40
Moisturising eye drops[13]	120 egtts	€ 44.67	€ 2.23	€ 2.38	€ 40.06	365.0	€ 365.55 – € 609.25
Ophthalmological base flat rate (FSI 06211 or FSI 06212)					€ 14.91 or € 17.33	1.0	€ 14.91 or € 17.33
Ophthalmological services (FSI 51050)					€ 15.12	1.0	€ 15.12
Abbreviations: Egtts = eye drops; SDP = single-dose pipettes							

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 1 October 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 agents a maximum amount of € 100 per ready-to-use preparation, and 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 Hilfstaxe.

[13] Fixed reimbursement rate

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 designate 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 approved 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 have 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 have 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.

Concomitant active ingredient

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 requirements 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 have 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 with disease progression on or after platinum-based first-line chemotherapy, who have not been pretreated with a PD-(L)1 antibody and who are eligible for further systemic, antineoplastic standard 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 approved in monotherapy.

b) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after

- platinum-free first-line chemotherapy without a PD-(L)1 antibody,
- first-line combination therapy consisting of chemotherapy and a PD-(L)1 antibody,
- sequential therapy with platinum-based chemotherapy and a PD-(L)1 antibody

who are eligible for further systemic, antineoplastic standard 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 approved in monotherapy.

c) Adult patients with recurrent or metastatic cervical cancer with disease progression on or after prior systemic therapy who are ineligible for further systemic, antineoplastic standard 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 approved in monotherapy.

Product information for tisotumab vedotin (Tivdak); Tivdak 40 mg powder for a concentrate for the preparation of an infusion solution; last revised: 06/2025

2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Tivdak is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV.

Approval studies include all studies submitted to the regulatory authority in section 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) of the authorisation dossier in the therapeutic indication for which marketing authorisation has been applied for. In addition, studies, which were conducted in whole or in part within the therapeutic indication described in this document, and in which the company was a sponsor or is otherwise financially involved, must also be indicated.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is < 5 per cent (2.1%) of the total number of study participants according to the information provided by the pharmaceutical company.

The pharmaceutical company provided information on seven studies (innovaTV 301, innovaTV 204, innovaTV 201, innovaTV 202, innovaTV 203, innovaTV 206, innovaTV 207) and stated that

the percentage of study participants at study sites within the scope of SGB V is 2.1% for all relevant studies. The information mainly refers to different phases of the studies mentioned, and this variation in the consideration of the study phases leads to uncertainty. In the IQWiG's assessment of the entire study populations across all phases of the respective studies, the percentage of study participants at study sites within the scope of SGB V remains below 5% of the total number of study participants.

The innovaTV 203 study was not included in the IQWiG's calculation because the study participants had already been included in the calculation as part of the innovaTV 201 and innovaTV 202 studies. In the Common Technical Document (CTD), another relevant study with registry entry (innovaTV 208), which was available to the regulatory authority during the marketing authorisation procedure, was identified. The study continued to show a percentage of less than 5% as there were no participants at German study sites.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant extent within the scope of SGB V.

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 their session on 12 March 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 August 2025, the pharmaceutical company submitted a dossier for the benefit assessment of tisotumab vedotin to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 August 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 tisotumab vedotin.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 November 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 December 2025. The deadline for submitting written statements was 22 December 2025.

The oral hearing was held on 12 January 2026.

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 subcommittee session on 10 February 2026, and the draft resolution was approved.

At their session on 19 February 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 March 2024	Determination of the appropriate comparator therapy
Working group Section 35a	7 January 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	12 January 2026	Conduct of the oral hearing
Working group Section 35a	21 January 2026; 4 February 2026	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	10 February 2026	Concluding discussion of the draft resolution
Plenum	19 February 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 February 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken