Gemeinsamer Bundesausschuss

Justification

for 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
Pembrolizumab (new therapeutic indication: head and neck squamous cell carcinoma, PD-L1 expression, first-line, in combination with radiotherapy with or without concomitant cisplatin therapy)

From 21 May 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,

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 active ingredient pembrolizumab (Keytruda) was listed for the first time on 15 August 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 24 October 2025, pembrolizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 20 November 2025, i.e. at the latest within four weeks of informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new therapeutic indication:

"KEYTRUDA® as monotherapy is indicated for the treatment of resectable locally advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 March 2026 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

Based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure as well as the addendum to the benefit assessment prepared by IQWiG, the G-BA decided on the question on whether an additional benefit of pembrolizumab compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. 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 IQWiG according to the General Methods was not used in the benefit assessment of pembrolizumab – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have come to the following assessment:

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

2.1.1 Approved therapeutic indication of Pembrolizumab (Keytruda) in accordance with the product information

KEYTRUDA® as monotherapy is indicated for the treatment of resectable locally advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1.

Therapeutic indication of the resolution (resolution of 21.05.2026):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

Appropriate comparator therapy:
A therapy regimen consisting of
- surgery (tumour resection)
- followed by an individualised therapy with selection of:
    - adjuvant chemoradiotherapy with cisplatin and
    - adjuvant radiotherapy

b) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

Appropriate comparator therapy:

A therapy regimen consisting of:
- surgery (tumour resection)
- followed by an individualised therapy with selection of:
    - adjuvant chemoradiotherapy with:
        - mitomycin + 5-FU

        or

        - Carboplatin + 5-FU

        or

        - docetaxel

    and
    - adjuvant radiotherapy

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 according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.

2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
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.

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

On 1. In addition to pembrolizumab, medicinal products with the active ingredients carboplatin, cisplatin, cetuximab, bleomycin and docetaxel are approved in the present therapeutic indication.

On 2. Surgery and radiotherapy are generally considered as non-medicinal treatments.

On 3. No corresponding resolutions are available.

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").

According to these guidelines, various treatment strategies are possible for patients with locally advanced head and neck squamous cell carcinoma. The guidelines recommend a primary surgical procedure followed by adjuvant radiotherapy or chemoradiotherapy for the patients addressed here with resectable, locally advanced stage III-IVA head and neck squamous cell carcinoma. The guidelines do not attribute any significance to neoadjuvant therapy for the treatment of resectable, locally advanced head and neck squamous cell carcinoma. This is consistent with the present statements made by scientific-medical societies on the issue of comparator therapy that the therapy standard is resection followed by indication-based radiotherapy or chemoradiotherapy, and that, where surgical procedure is planned, there is currently no indication for neoadjuvant therapy or induction chemotherapy.

Based on the available evidence, the choice between adjuvant radiotherapy or adjuvant chemoradiotherapy should be made depending on the postoperative risk profile of the patients.

Chemoradiotherapy is recommended for a high postoperative risk profile while adjuvant radiotherapy is recommended for a low postoperative risk profile.

The active ingredient cisplatin is recommended as the medicinal component for chemoradiotherapy in the case of high postoperative risk profile.

There are also recommendations for adjuvant chemoradiotherapy for patients with a high postoperative risk profile who are ineligible for cisplatin-based therapy. For these patients, the active ingredients carboplatin, cetuximab and bleomycin are approved for use as adjuvant treatment. However, the S3 guideline on oropharyngeal and hypopharyngeal carcinoma[1] does not recommend these approved active ingredients, or recommends them in a different combination. Instead, the guideline recommends mitomycin + 5-FU, carboplatin + 5-FU or docetaxel. According to the guideline, only minimal data are available on postoperative chemoradiotherapy for patients who, for example, cannot receive cisplatin due to impaired renal function. According to the guideline, data on mitomycin C are available from two small randomised studies, which have shown only a trend towards a survival benefit[2,3]. In a randomised study, the weekly administration of docetaxel in combination with simultaneous radiotherapy was compared with radiotherapy alone, in accordance with the guideline[4]. In a small subgroup of this study, treatment was also administered in the postoperative setting. According to the guideline, the combined therapy showed a trend towards improved survival. No results on carboplatin + 5-FU and carboplatin + paclitaxel are available from

[1] Oncology guideline programme (German Cancer Society (DKG), German Cancer Aid (DKH), Association of the Scientific-Medical Societies (AWMF)). Diagnosis, treatment, prevention and after-care for oropharyngeal and hypopharyngeal carcinoma; S3 guideline, long version [online]. AWMF registry number 017-082OL. Berlin (GER): Oncology guideline programme; 2024. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Oro-_und_Hypopharynxkarzinom/LL_Oro-_und_Hypopharynxkarzinom_Langversion_1.0.pdf.

[2] Weissberg JB, Son YH, Papac RJ, Sasaki C, Fischer DB, Lawrence R, Rockwell S, Sartorelli AC, Fischer JJ. Randomised clinical trial of mitomycin C as an adjunct to radiotherapy in head and neck cancer. Int J Radiat Oncol Biol Phys. 1989 Jul;17(1):3-9. doi: 10.1016/0360-3016(89)90362-3. PMID: 2501243.

[3] Haffty BG, Son YH, Sasaki CT, Papac R, Fischer D, Rockwell S, Sartorelli A, Fischer JJ. Mitomycin C as an adjunct to postoperative radiation therapy in squamous cell carcinoma of the head and neck: results from two randomised clinical trials. Int J Radiat Oncol Biol Phys. 1993 Sep 30;27(2):241-50. doi: 10.1016/0360-3016(93)90234-m. PMID: 7691784.

[4] Patil VM, Noronha V, Menon N, Singh A, Ghosh-Laskar S, Budrukkar A, Bhattacharjee A, Swain M, Mathrudev V, Nawale K, Balaji A, Peelay Z, Alone M, Pathak S, Mahajan A, Kumar S, Purandare N, Agarwal A, Puranik A, Pendse S, Reddy Yallala M, Sahu H, Kapu V, Dey S, Choudhary J, Krishna MR, Shetty A, Karuvandan N, Ravind R, Rai R, Jobanputra K, Chaturvedi P, Pai PS, Chaukar D, Nair S, Thiagarajan S, Prabhash K. Results of Phase III Randomised Trial for Use of Docetaxel as a Radiosensitiser in Patients With Head and Neck Cancer, Unsuitable for Cisplatin-Based Chemoradiation. J Clin Oncol. 2023 May 1;41(13):2350-2361. doi: 10.1200/JCO.22.00980. Epub 2023 Jan 27. PMID: 36706347.

randomised studies in the postoperative setting. However, in line with the guideline, it seems reasonable to use these combinations in the postoperative setting as well, based on the efficacy of these combinations in primary chemoradiotherapy. According to the guideline, no data are available to suggest that the use of cetuximab in the postoperative setting is beneficial.

In the overall assessment, according to the generally recognised state of medical knowledge, the G-BA assume that the off-label use of mitomycin + 5-FU or carboplatin + 5-FU or docetaxel shall generally be preferred to the medicinal products previously approved in the therapeutic indication for the relevant patient group of adults with resectable, locally advanced head and neck squamous cell carcinoma (stage III-IVA) who have a high postoperative risk profile and are ineligible for cisplatin-based therapy (Section 6, paragraph 2, sentence 3, number 3 AM-NutzenV).

Patients can be divided according to their suitability for cisplatin-based chemotherapy prior to surgery, whereas an assessment of their risk profile can only be carried out after surgery.

In G-BA's view, according to the current state of medical knowledge, the present therapeutic indication comprises separate patient populations that should be considered individually and that differ in terms of treatment situation according to cisplatin eligibility. When determining the appropriate comparator therapy, a differentiation is thus made according to the following patient populations:

a) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

The G-BA determined a therapy regimen consisting of surgery (tumour resection) followed by an individualised therapy with selection of adjuvant chemoradiotherapy with cisplatin and adjuvant radiotherapy as the appropriate comparator therapy for adults with resectable, locally advanced head and neck squamous cell carcinoma (stage III–IVA), who are eligible for cisplatin-based therapy, taking into account their postoperative risk profile.

For the implementation of individualised therapy in a direct comparator study, it is expected that investigators will have a choice of several treatment options that will allow an individualised treatment decision to be made, taking into account the mentioned criteria (multi-comparator study).

b) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

The G-BA determined the appropriate comparator therapy to be a therapy regimen consisting of surgery (tumour resection) followed by an individualised adjuvant therapy with selection of radiotherapy with chemotherapy (mitomycin + 5-FU or carboplatin + 5-FU or docetaxel) and radiotherapy alone, taking into account the postoperative risk profile.

For the implementation of individualised therapy in a direct comparator study, it is expected that investigators will have a choice of several treatment options that will

allow an individualised treatment decision to be made, taking into account the mentioned criteria (multi-comparator study).

With regard to the surgery (tumour resection), it is assumed that, where indicated, this may also involve a neck dissection. It is also assumed that the possibility of a secondary resection will be assessed, where appropriate, and carried out, if indicated.

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

In the originally determined appropriate comparator therapy, patient groups a and b were distinguished by their postoperative risk profile.

During the written statement procedure, it was pointed out that the suitability of patients for cisplatin can be determined prior to surgery, whereas their postoperative risk profile can only be established after surgery.

Consequently, the patient group designations will be amended so that the only distinction made is based on suitability for a cisplatin-based chemotherapy.

The various treatment options available after surgery, taking into account the risk profile, are reflected in the newly determined appropriate comparator therapy for the two patient groups through the use of adjuvant individualised therapy with selection of radiotherapy alone and chemoradiotherapy.

Consequently, adjuvant radiotherapy was newly included as the appropriate comparator therapy for patient group b.

The present assessment of the additional benefit of pembrolizumab in this therapeutic indication remains unaffected by this change in the appropriate comparator therapy.

2.1.3 Extent and probability of the additional benefit

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

a) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

Hint for a minor additional benefit

b) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

An additional benefit is not proven.

Justification:

KEYNOTE 689 study

The KEYNOTE 689 study is an ongoing, multicentre, open-label, randomised, controlled phase III study, in which pembrolizumab as neoadjuvant therapy and as postoperative adjuvant therapy in combination with radiotherapy, with or without concomitant cisplatin therapy, followed by pembrolizumab monotherapy, is compared with postoperative adjuvant radiotherapy, with or without concomitant cisplatin therapy, in adult patients with resectable, locally advanced head and neck squamous cell carcinoma.

Adult patients with histologically confirmed, newly diagnosed, resectable, locally advanced head and neck squamous cell carcinoma, regardless of PD-L1 status, were enrolled in the study. They had to have a corresponding stage III or IVA carcinoma. At the time of enrolment in the study, the patients had to have an ECOG-PS of 0 or 1.

In the KEYNOTE 689 study, a total of 714 patients were randomised in a 1:1 ratio to the study arms (N = 363 vs N = 351). Randomisation was stratified by localisation of the primary tumour (oropharynx/oral cavity vs larynx vs hypopharynx), tumour stage (III vs IVA) and PD-L1 tumour proportion score (TPS) status (TPS ≥ 50% vs TPS < 50%).

In addition to the primary endpoint of event-free survival (EFS), overall survival and endpoints in the categories of morbidity, health-related quality of life and side effects were assessed. The results of the KEYNOTE 689 study as of the 1st data cut-off from 25.07.2024 were used for the benefit assessment.

Limitations of the KEYNOTE 689 study

In the study, the decision to administer adjuvant cisplatin therapy in addition to adjuvant radiotherapy was based on the postoperative risk, thus in accordance with the requirements for the appropriate comparator therapy. A high postoperative risk is defined as positive resection margins (< 1 mm of the primary resectate) or extranodal spread of the squamous cell carcinoma beyond the lymph node capsule.

However, this definition differs from the applicable guideline recommendations. The S3 guideline on oral, oropharyngeal and hypopharyngeal carcinoma recommends adjuvant cisplatin administration not only in cases of extranodal spread, but also where the resection margin < 5 mm in the primary resectate.

The pharmaceutical company's dossier does not include any data on how many of these patients had a resection margin < 5 mm in the primary resectate and for whom adjuvant cisplatin administration would have been indicated in accordance with the applicable guideline recommendations.

It can be assumed that some of the patients in the KEYNOTE 689 study were not treated in accordance with the guideline recommendations and were therefore potentially undertreated. It is unclear how this affects the results of the KEYNOTE 689 study. This aspect limits the transferability of the study results to the German healthcare context and is taken into account in the assessment of the reliability of data.

Extent and probability of the additional benefit

a) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

Mortality

Overall survival

Overall survival is a secondary endpoint in the KEYNOTE 689 study and is defined as the time between randomisation and death from any cause.

For the endpoint of overall survival, there was a statistically significant difference in favour of pembrolizumab, the extent of which was assessed as a relevant improvement, but no more than a minor improvement.

Morbidity

Failure of the curative therapeutic approach

Patients in the present therapeutic indication are treated with a curative therapeutic approach. The failure of a curative therapeutic approach is fundamentally patient-relevant.

In the dossier, the pharmaceutical company provide, on the one hand, analyses of the EFS endpoint in accordance with BICR. For these analyses, they provide information on the following qualifying events:

- Death
- Distant metastases
- Local progression and distant metastases
- Local progression/relapse

The qualifying events shown differ from the pre-specified EFS events according to the study protocol. Furthermore, it remains unclear how the qualifying events collected in the study according to the study protocol were matched to the qualifying events described in the dossier.

Furthermore, the dossier lacks information on how the 37 patients, who did not commence treatment after randomisation, were handled in the analyses.

In their statement in response to these points of criticism, the pharmaceutical company did not provide any further information on the EFS endpoint in accordance with the BICR. Solely

with regard to the "local progression" subcomponent did the pharmaceutical company clarify in the written statement procedure that the component of the EFS endpoint "radiological disease progression during the neoadjuvant phase that precludes surgery", introduced by Amendment 8 to the study protocol, was applied consistently and unconditionally to the entire data record. Radiological disease progression during the neoadjuvant phase, which did not prevent curative surgery, was not counted as an event. This procedure is appropriate.

Due to the described uncertainties regarding the qualifying events and the lack of information on patients who did not commence treatment after randomisation, the results for the EFS endpoint in accordance with the BICR are inappropriate and will not be used for the assessment.

In the dossier, the pharmaceutical company also presented an analysis which they describe as a post-hoc adapted EFS in accordance with BICR. In addition to the mentioned qualifying events of the EFS in accordance with the BICR, this also includes the following two components:

- No R0 resection
- No surgery

With regard to the analysis referred to in the dossier as "post-hoc adapted EFS", the pharmaceutical company point out in their statement that "no surgery" at the time of randomisation was considered to be a qualifying event for the 37 randomised but untreated patients (3 in the intervention arm vs 34 in the comparator arm). This is inappropriate, as it was known that some of these subjects had undergone surgery outside the scope of the study, or that further information on disease progression was available for these subjects, which could have been taken into account in the analyses. Given the significant imbalance between the intervention and comparator arms among patients who were not treated, assuming that an event occurred at the time of randomisation results in an unfair comparison.

With the sensitivity analyses 1 to 3 for the post-hoc adapted EFS, submitted as part of their statement, the pharmaceutical company address the aspect of randomised but untreated patients, and set out the qualifying events in detail. The mentioned subjects not being taken into account in the sensitivity analysis 1 is inappropriate as further information on disease progression is available for some of these patients. In the sensitivity analysis 3, an R0 resection was assumed for 6 of the 37 subjects who underwent surgery outside the scope of the study. The remaining 31 subjects were classified based on an EFS event at the latest possible time of surgery, which, likewise the analyses of the post-hoc adapted EFS, results in an unfair comparison. In the sensitivity analysis 2, successful surgery is assumed for all 37 subjects, provided that no EFS event occurred prior to the hypothetical surgery and no death was recorded. Patients are considered in the subsequent observation period, based on the available information on their disease progression.

Taken together, the analyses presented for the post-hoc adapted EFS, as well as associated sensitivity analyses 1 and 3, cannot be meaningfully interpreted due to the detailed assumptions regarding patients who did not commence treatment after randomisation; they are therefore not included in the assessment.

In contrast, the sensitivity analysis 2 is considered to be meaningfully interpretable with regard to the detailed assumptions.

Regardless of this, there is overarching uncertainty regarding the qualifying event "no R0 resection", which is taken into account in all analyses of the post-hoc adapted EFS, including the sensitivity analyses. In this regard, the following specific situation to this therapeutic indication must be taken into account: if tumour resection does not result in an R0 resection,

a cure can generally still be achieved through adjuvant chemoradiotherapy or adjuvant radiotherapy, both of which have a curative potential. Since adjuvant chemoradiotherapy or adjuvant radiotherapy forms part of the curative therapeutic approach in this therapeutic indication, the "no R0 resection" event does not necessarily imply failure of the curative therapeutic approach.

For the endpoint of post-hoc adapted EFS – sensitivity analysis 2, there was a statistically significant difference between the treatment groups to the advantage of pembrolizumab, both in the time-to-event analysis and in the event rate. The "no R0 resection" event significantly influences the effect in the composite endpoint: without this event, there is no statistically significant difference between the treatment groups in terms of the event rate. Due to the lack of required data, it is not possible to assess the impact of the "no R0 resection" event on the effect estimator of the corresponding time-to-event analysis.

Given the described uncertainty in the various analyses of the EFS presented above, the results on EFS are unsuitable for reliably indicating the failure of the curative therapeutic approach, and are not used for the assessment. No suitable data on the failure of the curative therapeutic approach are therefore available.

Symptomatology

EORTC QLQ-C30 and EORTC QLQ-H&N35

Symptomatology was assessed in the KEYNOTE 689 study using the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires.

According to the study protocol, patient-reported endpoints in the intervention arm were to be assessed on day 1 after randomisation (at baseline), during the neoadjuvant phase at week 4, and prior to surgery at week 6. Although the baseline assessment in the comparator arm was also scheduled for day 1 after randomisation, it could also be carried out within 4 weeks prior to surgery. Consequently, the timing of the baseline assessment could vary by up to 4 weeks between the study arms. In both study arms, further assessments were carried out during the adjuvant phase, with radiotherapy commencing at week 1 and week 4. Further assessments were carried out 12 weeks after the end of radiotherapy, and then every 3 months until the end of the 3rd study year and annually until the end of the 5th study year.

With regard to the analyses presented, significant uncertainty arises from the fact that the data collection is linked to treatment phases, whilst therapy regimens differ between study arms; as a result, patient-reported endpoints are not collected in parallel but at different points in time.

In order to enable analysis of the data collected despite the different data collection patterns, the pharmaceutical company have defined analysis time points, based on the data collection time points in the intervention arm. The data collection time points in the comparator arm were assigned to them. However, this assignment means that some of the information relating to individual data collection time points is lost, as they cannot be adequately assigned or the time interval between them is too high.

Overall, the results of the patient-reported endpoints on symptomatology are unsuitable for the assessment of the additional benefit due to the differences in data collection between the study arms, particularly at baseline.

Health status

EQ-5D VAS

The health status was assessed in the KEYNOTE 689 study using the EQ-5D visual analogue scale (VAS).

Due to the uncertainties described in the explanations on symptomatology, the results of the patient-reported endpoints on health status are unsuitable and are not used for the assessment.

Conclusion on morbidity

The results for both the EFS endpoint and the patient-reported endpoints on symptomatology and health status cannot be interpreted and are not used for the assessment. Consequently, no assessable data are available for the morbidity category.

Quality of life

EORTC QLQ-C30 and EORTC QLQ-H&N35

Quality of life was assessed in the KEYNOTE 689 study using the functional scales of the EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires.

Due to the uncertainties described in the explanations on symptomatology, the results of the patient-reported endpoints on health-related quality of life are unsuitable.

Side effects

The pharmaceutical company presented time-to-event analyses for the evaluations of the endpoint category of side effects, as the additional neoadjuvant and adjuvant administration of pembrolizumab in the intervention arm results in significantly different durations of observation between the treatment arms.

However, due to the study design, it should also be borne in mind that patients in the comparator arm undergo surgery earlier and start adjuvant therapy earlier than those in the intervention arm. As a result, adverse events associated with the surgery and adjuvant (chemo)radiotherapy occur earlier in the comparator arm, but not consistently at a different frequency than in the intervention arm.

Overall, the time lag between events in the intervention and control groups may lead to effect estimators in the time-to-event analyses presented by the pharmaceutical company; these estimators may not be plausible in the present add-on therapy with pembrolizumab in the adjuvant treatment, and therefore cannot be reliably interpreted as an advantage or a disadvantage.

Total adverse events (AEs)

In the KEYNOTE 689 study, an AE occurred in almost all patients in both study arms. The results are only presented additionally.

Serious AEs (SAEs), discontinuation due to AEs

Based on the time-to-event analysis, there was no statistically significant difference between the study arms for the endpoints of SAEs and discontinuation due to AEs.

However, the Kaplan-Meier curves each show a crossing pattern, meaning that the proportional-hazards assumption is not met and the hazard ratio cannot be interpreted.

Furthermore, with durations of observation differing between the treatment arms, significantly more events were observed in the intervention arm than in the comparator arm in each case; consequently, a potential disadvantage of pembrolizumab cannot be ruled out in any of these instances.

Severe AEs

For the endpoint of severe AEs, the time-to-event analysis showed a statistically significant difference between the study arms in favour of pembrolizumab.

When interpreting this result, it should however be borne in mind that the corresponding Kaplan-Meier curves show an almost parallel and only time-shifted trend, and that the event rates in both study arms are approximately the same.

The statistically significant difference is therefore based on a later onset of severe AEs; consequently, taking into account the above comments on the time lag between events in the intervention and control groups, no advantage of pembrolizumab can be derived in the overall analysis of the results for this endpoint.

Specific AEs

For each of the endpoints of immune-mediated SAEs and immune-mediated severe AEs, there was a statistically significant difference in terms of the relative risk between the study arms to the disadvantage of pembrolizumab. The disadvantages are not reflected in the overall rates for SAEs, severe AEs and discontinuation due to AEs.

Conclusion on side effects

The results of the respective time-to-event analyses for the endpoints of serious AEs and discontinuation due to AEs cannot be interpreted because the proportional-hazards assumption was not met in each case.

The statistically significant difference in favour of pembrolizumab observed in the time-to-event analysis for the endpoint of severe AEs is based solely on a later onset of severe AEs; consequently, no advantage of pembrolizumab is derived in the overall analysis of the results for this endpoint.

In the category of side effects, neither an advantage nor a disadvantage is identified overall.

<u>Overall assessment</u>

Results on mortality, morbidity, health-related quality of life and side effects from the KEYNOTE 689 study are available for the assessment of the additional benefit of pembrolizumab as monotherapy for the treatment of resectable locally advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1.

For the endpoint of overall survival, there was a statistically significant difference in favour of pembrolizumab, the extent of which was assessed as a relevant improvement, but no more than a minor improvement.

In the endpoint category of morbidity, no suitable data are available for the endpoint of symptomatology, assessed using the EORTC QLQ-C30 and EORTC QLQ-H&N35, and health status, assessed using the EQ-5D VAS, due to significant differences in the surveys between the study arms, particularly at baseline.

The results for the endpoint of event-free survival (EFS) are unsuitable to demonstrate the failure of the curative therapeutic approach with sufficient certainty.

Consequently, no assessable data are available for the morbidity category overall.

With regard to health-related quality of life (assessed using the EORTC QLQ-C30 and EORTC QLQ-H&N35), no suitable data are available due to significant differences in the surveys between the study arms, particularly at baseline.

With regard to the endpoints on side effects, the results from the respective time-to-event analyses for the endpoints of serious AEs and discontinuation due to AEs cannot be interpreted because the proportional-hazards assumption was not met in each case. The statistically significant difference in favour of pembrolizumab observed in the time-to-event analysis for the endpoint of severe AEs is based solely on a later onset of severe AEs; consequently, no advantage of pembrolizumab is derived in the overall analysis based solely on this result. In the category of side effects, neither an advantage nor a disadvantage is identified overall.

The overall analysis showed an advantage in terms of overall survival, the extent of which is considered a significant improvement. No suitable data to substantiate the failure of the curative therapeutic approach are available. Similarly, no suitable data on other patient-relevant endpoints of morbidity and health-related quality of life are available. The available data on side effects are only assessable to a limited extent. In the overall analysis, these limitations however do not call into question the advantage in terms of overall survival. Overall, the G-BA conclude a minor additional benefit of pembrolizumab for the treatment of resectable locally advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1 compared with postoperative adjuvant radiotherapy with or without concomitant cisplatin therapy.

Reliability of data (probability of additional benefit)

The randomised, multicentre, controlled KEYNOTE 689 study forms the basis of the present benefit assessment.

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

There is a high risk of bias in the results for the endpoint of overall survival. The reason for this is the lack of adjustment for PD-L1 status (TPS ≥
50% vs TPS < 50%) in the analyses presented for overall survival, contrary to the requirements in the study documents, meaning that result-oriented reporting for the endpoint of overall survival cannot be ruled out.

The risk of bias in the results for the endpoints on side effects is estimated to be high especially because the time lag between the events relating to side effects in the intervention group and the control group leads to effect estimators in the presented time-to-event analyses that may not be plausible in the present add-on therapy with pembrolizumab and therefore cannot be reliably interpreted as an advantage or disadvantage.

Furthermore, it remains unclear whether the results of the KEYNOTE 689 study can be unconditionally transferred to the German healthcare context, as the definition of a high postoperative risk of recurrence in the study differs from the guideline recommendations applicable in Germany.

In summary, the G-BA derive a hint for the identified additional benefit with regard to the reliability of data.

b) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

No data are available to allow an assessment of the additional benefit. In their dossier, the pharmaceutical company only presented data on the sub-population of patients who are eligible for cisplatin-based therapy (patient population a).

2.1.4 Summary of the assessment

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

"KEYTRUDA® as monotherapy is indicated for the treatment of resectable locally advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1."

The pharmaceutical company presented the results of the KEYNOTE 689 study for the benefit assessment.

The G-BA carried out separate assessments of the additional benefit depending on the suitability of patients for cisplatin-based therapy as part of adjuvant treatment:

a) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

   The G-BA determined the appropriate comparator therapy to be a therapy regimen consisting of

   - surgery (tumour resection)
   - followed by an individualised therapy with selection of:
     - adjuvant chemoradiotherapy with cisplatin and
     - adjuvant radiotherapy

   .

For the endpoint of overall survival, there was a statistically significant difference in favour of pembrolizumab, the extent of which was assessed as a relevant improvement, but no more than a minor improvement.

In the endpoint category of morbidity, no suitable data are available for the endpoint of symptomatology, assessed using the EORTC QLQ-C30 and EORTC QLQ-H&N35, and health status, assessed using the EQ-5D VAS, due to significant differences in the surveys between the study arms, particularly at baseline.

The results for the endpoint of event-free survival (EFS) are unsuitable to demonstrate the failure of the curative therapeutic approach with sufficient certainty.

Consequently, no assessable data are available for the morbidity category.

With regard to health-related quality of life (assessed using the EORTC QLQ-C30 and EORTC QLQ-H&N35), no suitable data are available due to significant differences in the surveys between the study arms, particularly at baseline.

With regard to the endpoints on side effects, the results from the respective time-to-event analyses for the endpoints of serious AEs and discontinuation due to AEs cannot be interpreted because the proportional-hazards assumption was not met in each case. The statistically significant difference in favour of pembrolizumab observed in the time-to-event analysis for the endpoint of severe AEs is based solely on a later onset of severe AEs; consequently, no advantage of pembrolizumab is derived in the overall analysis based solely

on this result. In the category of side effects, neither an advantage nor a disadvantage is identified overall.

In the overall analysis, the limitations arising from the available data basis do not call into question the advantage in terms of overall survival. Overall, the G-BA conclude a minor additional benefit of pembrolizumab as monotherapy for neoadjuvant treatment followed by adjuvant treatment in combination with radiotherapy, with or without concomitant cisplatin therapy, and then as monotherapy, compared with the corresponding therapy regimen without pembrolizumab.

The reliability of data of the additional benefit identified is classified in the "hint" category.

b) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

No data are available to allow an assessment of the additional benefit. In their dossier, the pharmaceutical company only presented data on the sub-population of patients who are eligible for cisplatin-based therapy (patient population a).

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).

Based on the information sources provided by the pharmaceutical company, the following adjustments were made to the calculation of patient numbers as part of the benefit assessment:

- When calculating the lower limit for patients with resectable stage III to IV disease, the percentage calculated in the benefit assessment slightly differs from the percentage provided by the pharmaceutical company.
- As the research questions are no longer categorised according to the presence of a high or low risk profile following the change to the appropriate comparator therapy, the corresponding calculation step is omitted (steps 8a and 8b1 from the benefit assessment). The value of 86% reported in the study by Hering et al. (2025) was also used as the basis for determining suitability for cisplatin.
- The patient numbers for patient group b) were recalculated accordingly as part of the benefit assessment.

The patient numbers adjusted as part of the benefit assessment are 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 Keytruda (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 25 March 2026):

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

Therapy with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with head and neck tumours as well as ear, nose and throat (otorhinolaryngology) specialists and other doctors from other specialist groups participating in the Oncology Agreement.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on 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: 15 March 2026).

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

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 comorbidities) are not taken into account when calculating the annual treatment costs.

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

Surgery (tumour resection)

Due to the multitude of procedures involved and the resulting varied treatment plans to be individually specified, surgeries in this therapeutic indication differ from patient to patient and cannot therefore be quantified.

Postoperative radiotherapy

For postoperative radiotherapy, the S3 guideline[5] recommends a total dose of 45 to 60 Gy, administered in single doses of 1.8 Gy or 2 Gy 5 x a week using conventional fractionation. This results in 25 to 30 treatment days. To minimise side effects, postoperative radiotherapy is routinely carried out using IMRT techniques.

Postoperative chemoradiotherapy

For postoperative chemoradiotherapy, the S3 guideline[5] recommends a total dose of 54 to 60 Gy, administered in single doses of 2 Gy 5 x a week using conventional fractionation. This results in 27 to 30 treatment days. To minimise side effects, postoperative chemoradiotherapy is routinely carried out using IMRT techniques.

[5] S3 guideline "Diagnosis, Treatment, Prevention and After-care for Oropharyngeal and Hypopharyngeal Carcinoma" long version 1.0, March 2024, AWMF registry number: 017-082OL

Cisplatin

When cisplatin is used as part of combination therapy, the usual dose, according to the product information, is 20 mg/m² or more, administered once every 3 to 4 weeks; the S3 guideline[5] specifies the upper limit in this context a dose of 100 mg/m² once every 3 weeks.

Mitomycin + 5-FU, carboplatin + 5-FU and docetaxel have not been granted the marketing authorisation for the present therapeutic indication. For cost representation of the off-label use of these therapies, the G-BA take the sources referenced in the S3 guideline[5] as the basis[6,7,8,9,10,11,12]. A period of one year is assumed for calculating the costs of the off-label use of mitomycin + 5-FU, carboplatin + 5-FU and docetaxel.

Mitomycin + 5-FU[6,7]

When using mitomycin + 5-FU, the recommended dose range for mitomycin is 10 mg/m² BSA in a 35-day cycle[6,7] to 15 mg/m² BSA in a 42-day cycle[7].

When using mitomycin + 5-FU, the calculated dose range for FU is from 600 mg/m² BSA over 5 days (on day 1 - 5) in a 35-day cycle[6] to max. 1,500 mg/m² BSA over 4 days (day 1 – 4) in a 42-day cycle[7].

Carboplatin + 5-FU[8,9,10,11]

The literature contains varying information on the use of carboplatin + 5-FU. This information ranges from 70 mg/m² carboplatin and 600 mg/m² 5-FU on days 1 – 4 in a 21-day cycle[8,9] over 70 mg/m² carboplatin and 600 mg/m² 5-FU on days 1 – 5 in a 28-day cycle[11] up to 75 mg/m² carboplatin and 1,000 mg/m² 5-FU on the days 1 – 4 in a 28-day cycle[10].
For the use of carboplatin + 5-FU, this resulted in a calculated range with a lower limit of 70 mg/m² carboplatin and 600 mg/m² 5-FU on days 1 – 5 in a 28-day cycle[11] and an upper limit of 70 mg/m² carboplatin and 600 mg/m² 5-FU on days 1 – 4[8,9] of a 21-day cycle.

Docetaxel[12]

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6 Budach V et al. Hyperfractionated accelerated radiation therapy (HART) of 70.6 Gy with concurrent 5-FU/Mitomycin C is superior to HART of 77.6 Gy alone in locally advanced head and neck cancer: long-term results of the ARO 95-06 randomised phase III trial. Int J Radiat Oncol Biol Phys. 2015 Apr 1;91(5):916-24

7 Keane TJ et al. A randomised trial of radiation therapy compared to split course radiation therapy combined with mitomycin C and 5 fluorouracil as initial treatment for advanced laryngeal and hypopharyngeal squamous carcinoma. Int J Radiat Oncol Biol Phys. 1993 Mar 15;25(4):613-8

8 Denis F et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomised trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol. 2004 Jan 1;22(1):69-76

9 Bourhis J et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol. 2012 Feb;13(2):145-53

10 Fallai C et al. Long-term results of conventional radiotherapy versus accelerated hyperfractionated radiotherapy versus concomitant radiotherapy and chemotherapy in locoregionally advanced carcinoma of the oropharynx. Tumori. 2006 Jan-Feb;92(1):41-54

11 Semrau R et al. Efficacy of intensified hyperfractionated and accelerated radiotherapy and concurrent chemotherapy with carboplatin and 5-fluorouracil: updated results of a randomised multicentric trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2006 Apr 1;64(5):1308-16

12 Patil VM et al. Results of Phase III Randomised Trial for Use of Docetaxel as a Radiosensitiser in Patients with Head and Neck Cancer, Unsuitable for Cisplatin-Based Chemoradiation. J Clin Oncol. 2023 May 1;41(13):2350-2361

The literature describes a docetaxel dose of 15 mg/m² BSA administered once every 7 days, with the first dose to be given within the first 5 days following the start of radiotherapy[12].

Treatment period:

a) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Pembrolizumab (neoadjuvant treatment as monotherapy, followed by adjuvant treatment in combination with radiotherapy, with or without concomitant cisplatin administration, followed by treatment as monotherapy)				
Neoadjuvant treatment phase *(pembrolizumab monotherapy)*				
Pembrolizumab	1 x per 21-day cycle	2	1	2.0
	or			
	1 x per 42-day cycle	1	1	1.0
Surgery (tumour resection)				
Surgery (tumour resection)	Different from patient to patient			
Adjuvant treatment phase *(pembrolizumab in combination with radiotherapy, with or without concomitant cisplatin administration)*				
Pembrolizumab in combination with radiotherapy				
Pembrolizumab	1 x per 21-day cycle	3	1	3.0
	or			
	1 x per 42-day cycle	2	1	2.0
Radiotherapy	5 single doses per week in conventional fractionation	25 – 30	1	25 – 30
Pembrolizumab in combination with radiotherapy with concomitant cisplatin administration				
Pembrolizumab	1 x per 21-day cycle	3	1	3.0
	or			
	1 x per 42-day cycle	2	1	2.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Radiotherapy	5 single doses per week in conventional fractionation	27 - 30	1	27 - 30
Cisplatin	1 x per 21-day cycle	2	1	2.0
	or			
	1 x per 28-day cycle	2	1	2.0
Subsequent treatment as monotherapy				
Pembrolizumab	1 x per 21-day cycle	12.0	1	12.0
	or			
	1 x per 42-day cycle	5.5	1	5.5
Appropriate comparator therapy				
A therapy regimen consisting of surgery (tumour resection), followed by an individualised therapy with selection of adjuvant chemoradiotherapy with cisplatin and adjuvant radiotherapy				
Surgery (tumour resection)				
Surgery (tumour resection)	Different from patient to patient			
Individualised therapy with the selection of adjuvant chemoradiotherapy with cisplatin and adjuvant radiotherapy				
Adjuvant radiotherapy				
Radiotherapy	5 single doses per week in conventional fractionation	25 – 30	1	25 – 30
Adjuvant radiotherapy with cisplatin				
Radiotherapy	5 single doses per week in conventional fractionation	27 - 30	1	27 - 30
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 28-day cycle	13.0	1	13.0

b) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Pembrolizumab (neoadjuvant treatment as monotherapy, followed by adjuvant treatment in combination with radiotherapy without concomitant cisplatin administration, followed by treatment as monotherapy)				
Neoadjuvant treatment phase *(pembrolizumab monotherapy)*				
Pembrolizumab	1 x per 21-day cycle	2	1	2.0
	or			
	1 x per 42-day cycle	1	1	1.0
Surgery (tumour resection)				
Surgery (tumour resection)	Surgery (tumour resection)			
Adjuvant treatment phase *(pembrolizumab in combination with radiotherapy without concomitant cisplatin administration)*				
Pembrolizumab in combination with radiotherapy				
Pembrolizumab	1 x per 21-day cycle	3	1	3.0
	or			
	1 x per 42-day cycle	2	1	2.0
Radiotherapy	5 single doses per week in conventional fractionation	25 – 30	1	25 – 30
Subsequent treatment as monotherapy				
Pembrolizumab	1 x per 21-day cycle	12.0	1	12.0
	or			
	1 x per 42-day cycle	5.5	1	5.5
Appropriate comparator therapy				
A therapy regimen consisting of surgery (tumour resection), followed by an individualised therapy with selection of adjuvant chemoradiotherapy with mitomycin + 5-FU or carboplatin + 5-FU or docetaxel, and adjuvant radiotherapy				
Surgery (tumour resection)				
Surgery (tumour resection)	Different from patient to patient			

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Individualised therapy with the selection of adjuvant chemoradiotherapy with mitomycin + 5-FU or carboplatin + 5-FU or docetaxel*, and adjuvant radiotherapy*				
Adjuvant radiotherapy				
Radiotherapy	5 single doses per week in conventional fractionation	25 – 30	1	25 – 30
Adjuvant radiotherapy in combination with mitomycin + 5-FU[6,7]				
Radiotherapy	5 single doses per week in conventional fractionation	27 - 30	1	27 - 30
Mitomycin	1 x per 35-day cycle[6]	10.4	1	10.4
	or			
	1 x per 42-day cycle[7]	8.7	1	8.7
5-FU	1 x on day 1 – 5 per 35-day cycle[6]	10.4	5	52.0
	or			
	1 x on day 1 – 4 per 42-day cycle[7]	8.7	4	34.8
Adjuvant radiotherapy in combination with carboplatin + 5-FU[8,9,11]				
Radiotherapy	5 single doses per week in conventional fractionation	27 - 30	1	27 - 30
Carboplatin	1 x on day 1 – 5 per 28-day cycle[11]	13.0	5	65.0
	or			
	1 x on day 1 – 4 per 21-day cycle[8,9]	17.4	4	69.9
5-FU	1 x on day 1 – 4 per 21-day cycle[8,9]	17.4	4	69.9
	or			
	1 x on day 1 – 5 per 28-day cycle[11]	13.0	5	65.0
Adjuvant radiotherapy in combination with docetaxel[12]				
Radiotherapy	5 single doses per week in conventional fractionation	27 - 30	1	27 - 30
docetaxel	1 x per 7-day cycle[12]	52.1	1	52.1

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

The (daily) doses recommended in the product information were used as the calculation basis.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[13].

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.

a) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

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					
Pembrolizumab (neoadjuvant treatment as monotherapy, followed by adjuvant treatment in combination with radiotherapy, with or without concomitant cisplatin administration, followed by treatment as monotherapy)					
Neoadjuvant treatment phase *(pembrolizumab monotherapy)*					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	2.0	4.0 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	1.0	4.0 x 100 mg
Surgery (tumour resection)					
Surgery (tumour resection)	Surgery (tumour resection)				
Adjuvant treatment phase *(pembrolizumab in combination with radiotherapy, with or without concomitant cisplatin administration)*					
Pembrolizumab in combination with radiotherapy					

[13] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Pembrolizumab	200 mg	200 mg	2 x 100 mg	3.0	6.0 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	2.0	8.0 x 100 mg
Radiotherapy	1.8 Gy – 2.0 Gy	1.8 Gy – 2.0 Gy	1.8 Gy – 2.0 Gy	25 – 30	45 Gy – 60 Gy
Pembrolizumab in combination with radiotherapy with concomitant cisplatin administration					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	3.0	6.0 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	2.0	8.0 x 100 mg
Radiotherapy	2.0 Gy	2.0 Gy	2.0 Gy	27 – 30	54 Gy – 60 Gy
Cisplatin	20 mg/m^2 BSA = 38.2 mg	38.2 mg	1 x 50 mg	2.0	2.0 x 50 mg
	or				
	100 mg/m^2 BSA = 191.0 mg	191.0 mg	2 x 100 mg	2.0	4.0 x 100 mg
Subsequent treatment as monotherapy					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	12.0	24.0 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	5.5	22.0 x 100 mg
Appropriate comparator therapy					
A therapy regimen consisting of surgery (tumour resection), followed by an individualised therapy with selection of adjuvant chemoradiotherapy with cisplatin and adjuvant radiotherapy					
Surgery (tumour resection)					
Surgery (tumour resection)	Different from patient to patient				
Individualised therapy with the selection of adjuvant chemoradiotherapy with cisplatin and adjuvant radiotherapy					
Adjuvant radiotherapy					
Radiotherapy	1.8 Gy – 2.0 Gy	1.8 Gy - 2.0 Gy	1.8 Gy - 2.0 Gy	25 – 30	45 Gy – 60 Gy
Adjuvant radiotherapy with cisplatin					
Radiotherapy	2.0 Gy	2.0 Gy	2.0 Gy	27 – 30	54 Gy – 60 Gy
Cisplatin	20 mg/m^2 BSA	38.2 mg	1 x 50 mg	13.0	13.0 x 50 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	= 38.2 mg			– 17.4	– 17.4 x 50 mg
	or				
	100 mg/m² BSA = 191.0 mg	191.0 mg	2 x 100 mg	13.0 – 17.4	26.0 x 100 mg – 34.8 x 100 mg

b) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

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					
Pembrolizumab (neoadjuvant treatment as monotherapy, followed by adjuvant treatment in combination with radiotherapy without concomitant cisplatin administration, followed by treatment as monotherapy)					
Neoadjuvant treatment phase (pembrolizumab monotherapy)					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	2.0	4.0 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	1.0	4.0 x 100 mg
Surgery (tumour resection)					
Surgery (tumour resection)	Surgery (tumour resection)				
Adjuvant treatment phase (pembrolizumab in combination with radiotherapy, with or without concomitant cisplatin administration)					
Pembrolizumab in combination with radiotherapy					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	3.0	6.0 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	2.0	8.0 x 100 mg
Radiotherapy	1.8 Gy – 2.0 Gy	1.8 Gy -	1.8 Gy -	25 – 30	45 Gy – 60 Gy

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
		2.0 Gy	2.0 Gy		
Subsequent treatment as monotherapy					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	12.0	24.0 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	5.5	22.0 x 100 mg
Appropriate comparator therapy					
A therapy regimen consisting of surgery (tumour resection), followed by an individualised therapy with selection of adjuvant chemoradiotherapy with mitomycin + 5-FU or carboplatin + 5-FU or docetaxel, and adjuvant radiotherapy					
Surgery (tumour resection)					
Surgery (tumour resection)	Different from patient to patient				
Individualised therapy with the selection of adjuvant chemoradiotherapy with mitomycin + 5-FU or carboplatin + 5-FU or docetaxel*, and adjuvant radiotherapy*					
Adjuvant radiotherapy					
Radiotherapy	1.8 Gy – 2.0 Gy	1.8 Gy - 2.0 Gy	1.8 Gy - 2.0 Gy	25 – 30	45 Gy – 60 Gy
Adjuvant radiotherapy in combination with mitomycin + 5-FU[6,7]					
Radiotherapy	2.0 Gy	2.0 Gy	2.0 Gy	27 – 30	54 Gy – 60 Gy
Mitomycin	10 mg/m² BSA[6,7] = 19.1 mg - 15 mg/m² BSA[7] = 28.7 mg	19.1 mg - 28.7 mg	1 x 20 mg - 2 x 20 mg	10.4 - 8.7	8.7 - 10.4 x 20 mg - 17.4 – 20.8 x 20 mg
5-FU	600 mg/m² BSA[6] = 1,146 mg - 1,500 mg/m² BSA[7] = 2,865 mg	1,146 mg - 2,865 mg	2 x 1,000 mg - 3 x 1,000 mg	52.0 - 34.8	69.9 - 104 x 1,000 mg - 104.4 – 156 x 1,000 mg
Adjuvant radiotherapy in combination with carboplatin + 5-FU[8,9,11]					
Radiotherapy	2.0 Gy	2.0 Gy	2.0 Gy	27 – 30	54 Gy – 60 Gy
Carboplatin	70 mg/m² BSA[8,9,11] = 133.7 mg	133.7 mg	1 x 150 mg	65.0 - 69.6	65.0 x 150 mg - 69.6 x 150 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
5-FU	600 mg/m² BSA[8,9,11] = 1,146 mg	1,146 mg	2 x 1,000 mg	65.0 - 69.6	130.0 x 1,000 mg - 139.2 x 1,000 mg
Adjuvant radiotherapy in combination with docetaxel[12]					
Radiotherapy	2.0 Gy	2.0 Gy	2.0 Gy	27 – 30	54 Gy – 60 Gy
docetaxel	15 mg/m² BSA = 28.7 mg	28.7 mg	2 x 20 mg	52.1	104.2 x 20 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of radiotherapy

a) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
(Chemo)radiotherapy				
Radiotherapy with a linear accelerator for malignant diseases	Radiotherapy with a linear accelerator for malignant diseases or space-occupying processes of the central nervous system (FSI: 25321)	25 – 30	€ 122.31	€ 3,057.75 – € 3,669.30
		or		
		27 - 30	€ 122.31	€ 3,302.37 – € 3,669.30
MRI examination of the viscerocranium	MRI examination of the viscerocranium (FSI: 34420)	1	€ 134.16	€ 134.16

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
MRI examination of the soft tissues of the neck	MRI examination of the soft tissues of the neck (FSI: 34422)	1	€ 134.16	€ 134.16
Radiotherapy planning III	Computer-aided treatment planning for external beam radiotherapy with individual dose planning for irregular fields with individual blocks, multi-lamella collimator, non-coplanar fields and/or 3D planning (FSI: 25342)	1	€ 604.40	€ 604.40
Surcharge for high-precision radiotherapy planning	Surcharge for high-precision radiotherapy planning (IMRI and/or fractionated stereotaxy) (FSI: 25343)	1	€ 158.62	€ 158.62

b) <u>Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy</u>

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
(Chemo)radiotherapy				
Radiotherapy with a linear accelerator for malignant diseases	Radiotherapy with a linear accelerator for malignant diseases or space-occupying processes of the central nervous system (FSI: 25321)	25 – 30	€ 122.31	€ 3,057.75 – € 3,669.30
		or		
		27 - 30	€ 122.31	€ 3,302.37 – € 3,669.30
MRI examination of the viscerocranium	MRI examination of the viscerocranium (FSI: 34420)	1	€ 134.16	€ 134.16
MRI examination of the soft tissues of the neck	MRI examination of the soft tissues of the neck (FSI: 34422)	1	€ 134.16	€ 134.16
Radiotherapy planning III	Computer-aided treatment planning for external beam radiotherapy with individual dose planning for irregular fields with individual blocks, multi-lamella collimator, non-coplanar fields and/or 3D planning (FSI: 25342)	1	€ 604.40	€ 604.40

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
Surcharge for high-precision radiotherapy planning	Surcharge for high-precision radiotherapy planning (IMRI and/or fractionated stereotaxy) (FSI: 25343)	1	€ 158.62	€ 158.62

Costs of the medicinal products:

a) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

b) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

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					
Pembrolizumab 100 mg	2 CIS	€ 4,962.26	€ 1.77	€ 280.10	€ 4,680.39
Cisplatin 50 mg	1 CIS	€ 47.30	€ 1.77	€ 1.71	€ 43.82
Cisplatin 100 mg	1 CIS	€ 76.59	€ 1.77	€ 3.10	€ 71.72
Appropriate comparator therapy					
Carboplatin 150 mg	1 CIS	€ 83.04	€ 1.77	€ 3.40	€ 77.87
Cisplatin 50 mg	1 CIS	€ 47.30	€ 1.77	€ 1.71	€ 43.82
Cisplatin 100 mg	1 CIS	€ 76.59	€ 1.77	€ 3.10	€ 71.72
Docetaxel 20 mg	1 CIS	€ 112.47	€ 1.77	€ 4.80	€ 105.90
5-FU 1,000 mg	1 IIS	€ 16.67	€ 1.77	€ 0.42	€ 14.48
Mitomycin 20 mg	5 PII	€ 804.57	€ 1.77	€ 100.39	€ 702.41
Abbreviations: CIS = concentrate for the preparation of an infusion solution, SII = solution for injection/infusion, PII = powder for the preparation of a solution for injection/infusion, or powder and solvent for the preparation of a solution for intravesicular use					

LAUER-TAXE® last revised: 15 March 2026

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.

a) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

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

b) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

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).

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Cisplatin							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific details in this regard, which is why the necessary costs cannot be quantified.							
Medicinal product to be assessed:							
Hydration and forced diuresis 2 cycles							
Mannitol 10% Inf. sol., 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	2	€ 96.00
Sodium chloride 0.9% Inf. sol., 3 - 4.4 l/day	10 x 500 ml INF	€ 13.28	€ 0.66	€ 0.96	€ 11.66	2	€ 20.05
	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	2	
Appropriate comparator therapy:							
Hydration and forced diuresis 13.0 cycles							
Mannitol 10% Inf. sol., 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	13.0	€ 124.80
Sodium chloride 0.9% Inf. sol.,	10 x 500 ml INF	€ 13.28	€ 0.66	€ 0.96	€ 11.66	13.0	€ 78.20 -

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
3 - 4.4 l/day	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	13.0	€ 82.70
Hydration and forced diuresis 17.4 cycles							
Mannitol 10% Inf. sol., 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	17.4	€ 167.04
Sodium chloride 0.9% Inf. sol., 3 - 4.4 l/day	10 x 500 ml INF	€ 13.28	€ 0.66	€ 0.96	€ 11.66	17.4	€ 104.66 - € 159.84
	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	17.4	

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 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-apply unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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 data from the product 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 statutory 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) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are eligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

No medicinal product with new active ingredients for use in combination therapy in compliance with the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for pembrolizumab (Keytruda); Keytruda 25 mg/ml concentrate for the preparation of an infusion solution 100 mg/ 4 ml; last revised: November 2025

b) Adults with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 and who are ineligible for cisplatin-based therapy; neoadjuvant and adjuvant therapy

No medicinal product with new active ingredients for use in combination therapy in compliance with the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for pembrolizumab (Keytruda); Keytruda 25 mg/ml concentrate for the preparation of an infusion solution 100 mg/ 4 ml; last revised: November 2025

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 28 May 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products newly determined the appropriate comparator therapy at their session on 15 October 2025.

On 20 November 2025, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 17 October 2025 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 pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 February 2026, and the written statement procedure was initiated with publication on the G-BA website on 2 March 2026. The deadline for submitting statements was 23 March 2026.

The oral hearing was held on 7 April 2026.

By letter dated 8 April 2026, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 30 April 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 were discussed at the Subcommittee's session on 12 May 2026, and the draft resolution was deliberated.

At their session on 21 May 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	28 May 2024	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	15 October 2025	New determination of the appropriate comparator therapy
Working group Section 35a	1 April 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 April 2026	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 April 2026 6 May 2026	Consultation on the dossier assessment by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	12 May 2026	Concluding discussion of the draft resolution
Plenum	21 May 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 May 2026

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

Prof. Hecken