Gemeinsamer Bundesausschuss

# Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:

Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V

Nivolumab (new therapeutic indication: oesophageal or gastro-oesophageal junction cancer, pretreated patients, adjuvant treatment)

of 17 February 2022

**Contents**



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## 1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

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

On 28 July 2021, Opdivo 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, 12 December 2008, p. 7).

On 24 August 2021, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient nivolumab with the new therapeutic indication (adjuvant treatment of oesophageal or gastro-oesophageal junction cancer) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 December 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.



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

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

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

### 2.1.1 Approved therapeutic indication of Nivolumab (Opdivo) in accordance with the product information

Opdivo as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

**Therapeutic indication of the resolution (resolution of 17.02.2022):**

see the approved therapeutic indication

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with oesophageal or gastro-oesophageal junction cancer and residual pathologic disease following prior neoadjuvant chemoradiotherapy; adjuvant treatment

- Monitoring wait-and-see approach

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.



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

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

on 1. There are no approved medicinal products available for the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer.

on 2. A non-medicinal treatment cannot be considered as a comparator therapy in the planned therapeutic indication.

on 3. Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V:
- Ramucirumab: Resolution of 20 October 2016

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 § 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

For patients with oesophageal or gastro-oesophageal junction cancer and residual pathologic disease following prior neoadjuvant chemoradiotherapy, there are no approved medicinal products and also no recommendations in the guidelines for further adjuvant treatment with or without medicinal products. This applies to both squamous cell carcinomas and adenocarcinomas, regardless of histology. Since patients in the therapeutic indication are considered disease-free, the recommendations of the current guidelines are limited to symptom-oriented after-care with the goals of, among other things, recording functional disorders that affect quality of life and diagnosing recurrences at an early stage.

The scientific-medical societies also state in their written comments on the present procedure that adjuvant therapy is not part of the standard of care for patients with resected oesophageal or gastro-oesophageal junction cancer following prior neoadjuvant chemoradiotherapy. It is further stated that the after-care is usually symptom-oriented and that functional disorders should be detected, nutritional status checked and the need for psychosocial support evaluated. According to the scientific-medical societies, structured after-care is carried out in large centres in order to detect recurrences at an early stage.

Therefore, the G-BA has determined the "monitoring wait-and-see approach" as the appropriate comparator therapy.

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



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### 2.1.3 Extent and probability of the additional benefit

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

For the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer in adults with residual pathologic disease following prior neoadjuvant chemoradiotherapy, an indication of a non-quantifiable additional benefit is identified.

Justification:

For the proof of additional benefit of nivolumab for the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer in adults with residual pathologic disease following prior neoadjuvant chemoradiotherapy, the pharmaceutical company has submitted the results of the CA209-577 study.

CA209-577 is an ongoing, parallel, double-blind, randomised controlled phase III study comparing nivolumab to placebo.

The placebo comparison carried out corresponds to an implementation of the appropriate comparator therapy consisting of the monitoring wait-and-see approach.

The multicentre, international study included adults with stage II or III oesophageal or gastro-oesophageal junction cancer (classification according to the 7th edition of the American Joint Committee on Cancer) at initial diagnosis. Patients had to have completed neoadjuvant platinum-based chemoradiotherapy followed by resection and there had to be R0 resection with residual pathologic disease (≥ ypT1 or ≥ ypN1).

The patients had to have also a good general condition, with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1, and a disease-free status.

The 794 patients included were randomised 2: 1 into the nivolumab arm (N=532) and placebo arm (N=262), stratified by PD-L1 status (≥ 1 % vs < 1 % or indeterminate / not evaluable), pathological lymph node status (≥ ypN1 vs ypN0) and histology (squamous cell vs adenocarcinoma).

In addition to the primary endpoint of disease-free survival (DFS), endpoints of the categories mortality, morbidity, health-related quality of life and adverse events (AEs) were collected.

For the present benefit assessment, the data cut-off date of 18 February 2021 required by the European Medicines Agency (EMA) is used for the endpoints recurrence rate and disease-free survival, and for the other endpoints the planned 1st data cut-off from 3 July 2020 according to the study protocol.

Extent and probability of the additional benefit

Mortality

The pharmaceutical company does not provide any data on overall survival.

The pharmaceutical company justifies its action by stating that the first interim analysis (data cut-off from 3 July 2020) for overall survival was linked to the interim analysis for the primary endpoint disease-free survival (DFS) and was dependent on the achievement of the planned number of DFS events. As the planned event numbers and the specified significance level were not achieved for the first interim analysis as well as for the data cut-off required by EMA (18 February 2021), the overall survival data for the pharmaceutical company were not unblinded.

According to the IQWiG, the failure to unblind the overall survival data is not fully understandable, as the recurrence rate also includes the event "death without recurrence", for which unblinded data per treatment arm are available.



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The approach on the part of the pharmaceutical company is therefore viewed critically. Data on overall survival are considered particularly relevant in the assessment of the additional benefit of nivolumab in the treatment settings presented here. However, an assessment of the endpoint is not possible based on the pharmaceutical company's approach.

Morbidity

*Recurrences*

The endpoint recurrence, operationalised as recurrence rate, describes the percentage of patients with a recurrence event or death at the corresponding data cut-off (event rate). In the endpoint DFS, the time to the event (recurrence or death) is also considered (time-to-event analysis).

The combined endpoint recurrences include the following individual components:

- Local recurrence
- Regional recurrence
- Remote metastases
- Death without recurrence

*Recurrences (event rate)*

For the recurrence rate, there is a statistically significant difference in the benefit of nivolumab compared to the monitoring wait-and-see approach. The magnitude of this effect is judged to be an improvement in therapy-relevant benefit. At the time of the data cut-off, 50.4% of patients in the nivolumab arm and 65.3% of patients in the placebo arm had a recurrence. The endpoint recurrence rate includes the same individual components and thus the same recurrence events and deaths before recurrence events as other components like the endpoint DFS.

*Disease-free survival (DFS)*

The time-to-event analysis shows a statistically significant positive effect for nivolumab compared to the monitoring wait-and-see approach, which is assessed as a clinical improvement.

The overall assessment on recurrences shows a positive effect of nivolumab compared to the monitoring wait-and-see approach.

*Health status (assessed by EQ-5D VAS)*

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the benefit assessment, the pharmaceutical company submits responder analyses for this endpoint for the time to permanent deterioration by ≥ 7, ≥ 10 and ≥ 15 points respectively compared to baseline.

There was no statistically significant difference between the study arms for any of the evaluations presented.

An additional benefit of nivolumab for the endpoint health status (EQ-5D VAS) is not proven.

Quality of life

*FACT-E*

Health-related quality of life was assessed in the CA209-577 study using the FACT-E questionnaire. However, as only the FACT-G7 and the ECS, but no longer the full FACT-E, were



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collected in the survival follow-up, the responder analyses of the FACT-E total score, operationalised as time to permanent deterioration by 15 points, are used for the present benefit assessment.

There is no statistically significant difference between the treatment arms.

An additional benefit of nivolumab for the endpoint category quality of life (EQ-5D-VAS) is not proven.

Side effects

Endpoints in the category side effects were assessed up to 100 days after the end of treatment.

*Adverse events (AEs)*

In the CA209-577 study, 96.1% of patients in the intervention arm experienced an adverse event, compared to 92.7% of patients in the comparator arm. These are only presented additionally.

*Serious adverse events (SAEs) and severe AEs (CTCAE grade 3 or 4)*

For the endpoints SAEs and severe AEs (CTCAE grade ≥ 3), there were no statistically significant differences between nivolumab versus monitoring wait-and-see approach.

*Discontinuation due to AEs*

For the endpoint on therapy discontinuation due to AE, there was a statistically significant difference to the disadvantage of nivolumab.

*Specific AEs*

There are statistically significant disadvantages for nivolumab with regard to specific AEs. In detail, there are disadvantages with regard to the endpoints infections and infestations (severe AEs) and blood and lymphatic system disorders (severe AEs). For the endpoints immune-mediated SAEs and immune-mediated severe AE there was no statistically significant difference between the treatment arms.

In summary, a disadvantage for treatment with nivolumab can be identified because of the negative effect in therapy discontinuations due to AEs. With regard to specific adverse events, there are disadvantages for nivolumab in detail.

Overall assessment

For the assessment of the additional benefit of nivolumab, results are available from the CA209-577 study in comparison to monitoring wait-and-see approach regarding morbidity (health status), quality of life and side effects.

For the endpoint category mortality, no data from study CA209-577 were provided by the pharmaceutical company. However, data on overall survival are considered particularly relevant in the assessment of the additional benefit of nivolumab in the treatment setting presented here. Due to the lack of overall survival data, uncertainties remain due to a possible disadvantage of nivolumab versus monitoring wait-and-see approach.

In the endpoint category morbidity, nivolumab showed statistically significant advantages compared to the monitoring wait-and-see approach in terms of recurrence rate and disease-free survival. The avoidance of recurrences is patient-relevant in view of the present fundamentally curative therapy claim.

An additional benefit of nivolumab for the endpoint health status (EQ-5D VAS) is not proven.



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For health-related quality of life, assessed with the FACT-E total score, there is no statistically significant difference between the study arms.

In terms of side effects, for the endpoint discontinuation due to AEs, a disadvantage of nivolumab compared to the monitoring wait-and-see approach is observed. In detail, there are also disadvantages for nivolumab in the specific AEs. In the category of side effects, there are thus overall disadvantageous effects of nivolumab compared to the monitoring wait-and-see approach.

Overall, the positive effect on recurrences is offset by a disadvantage in terms of side effects. The disadvantage in the side effects category does not call into question the positive effect in terms of avoiding recurrences overall. However, due to the lack of data on overall survival and the resulting uncertainties, the additional benefit of nivolumab cannot be quantified.

In the overall assessment, therefore, for the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer in adults with residual pathologic disease following prior neoadjuvant chemoradiotherapy an indication of a non-quantifiable additional benefit is identified for nivolumab compared to the monitoring wait-and-see approach.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of one study. The CA209-577 study compared nivolumab to placebo in a randomised, controlled, double-blind comparison.

The risk of bias at study level is rated as low.

The endpoint risk of bias for the endpoint recurrence is rated as low. For the endpoint discontinuation due to AEs, the potential for bias is rated as low.

Overall, an indication is derived for the reliability of data.

### 2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the present benefit assessment of nivolumab finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

Due to the lack of results on overall survival, the significance is limited and uncertainties remain.

Since further clinical data from the CA209-577 study are expected, which are relevant for evaluating the benefits of the medicinal product, it is justified to limit the validity of the present resolution.

Conditions of the limitation:

For the new benefit assessment of nivolumab after the deadline, the results on all patient-relevant endpoints from the CA209-577 study must be submitted in the dossier by 1 October 2024. By the time the limitation expires, the data from the final data cut-off after the occurrence of 460 events in overall survival should be submitted. If the final data are not yet available at the time of the expiry of the limitation, the data of a current interim analysis, which is not older than 6 months, on all patient-relevant endpoints from the CA209-577 study must be submitted to the G-BA.

For this purpose, the G-BA considers a limitation for the resolution until 1 October 2024 to be appropriate.



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A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product nivolumab recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of nivolumab in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). The possibility that a benefit assessment for the medicinal product nivolumab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

### 2.1.5 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient nivolumab. The therapeutic indication assessed here is as follows: Opdivo as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

The monitoring wait-and-see approach was determined as the appropriate comparator therapy.

For the benefit assessment of nivolumab, data on morbidity, quality of life and side effects are available from the CA209-577 study.

No data were presented for the endpoint overall survival. However, these are considered to be particularly relevant in the assessment of the additional benefit in the treatment setting presented here.

For the endpoints recurrence rate and disease-free survival, there are statistically significant advantages for nivolumab compared to the monitoring wait-and-see approach. The avoidance of recurrences is patient-relevant in view of the present fundamentally curative therapy claim.

An additional benefit of nivolumab for the endpoint health status (EQ-5D-VAS) and for quality of life (FACT-E total score) is not proven.

In terms of side effects, there are disadvantages of nivolumab with regard to the endpoint discontinuation due to AEs and in detail with regard to the specific AEs. No differences are seen for serious adverse events and severe AEs (CTCAE grade 3 or 4). In the category of side effects, there are thus overall disadvantageous effects of nivolumab.

Overall, the positive effect on recurrences is offset by a disadvantage in terms of side effects. The disadvantage in terms of side effects does not call into question the positive effect in terms of avoiding recurrences overall. However, due to the lack of data on overall survival and the resulting uncertainties, the additional benefit of nivolumab cannot be quantified.

In the overall assessment, therefore, an indication of a non-quantifiable additional benefit over the monitoring wait-and-see approach is established for nivolumab.

Due to the low risk of bias in the endpoint's recurrences and therapy discontinuations, an indication is derived for the reliability of data.

The resolution for this group of patients is limited until 1 October 2024.



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

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

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier. The information is subject to uncertainties. For example, it is uncertain to what extent the percentage for neoadjuvant chemoradiotherapy and resection deviate if patients are also taken into account for whom no information on treatment is yet available and to what extent they deviate for the year 2021 compared to the year 2018. Furthermore, the range includes an unknown number of patients with ≥ R1 resection who are not included in the therapeutic indication.

## 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 Opdivo (active ingredient: nivolumab) at the following publicly accessible link (last access: 2 February 2022):

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

Treatment with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology, oncology and gastroenterology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with oesophageal carcinoma.

In accordance with the Medicines Agency requirements regarding additional risk minimisation measures, the pharmaceutical company must provide healthcare professionals and patients with a patient card. The patient card contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with nivolumab as well as on infusion-related reactions. The prescribing doctors must discuss the risks of therapy with nivolumab with the patients.

## 2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2022).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The use of nivolumab as adjuvant treatment is limited to 12 months.



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| Designation of the therapy | Treatment mode | Number of treatments/ patient /year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Nivolumab | | | | |
| Initial treatment (week 1-16) | 1 x per 14 day cycle | 8.0 | 1 | 8.0 |
| | or | | | |
| | 1 x per 28 day cycle | 4.0 | 1 | 4.0 |
| Follow-up treatment (from week 17) | 1 x per 28 day cycle | 9.0 | 1 | 9.0 |
| Appropriate comparator therapy | | | | |
| Monitoring wait-and-see approach | incalculable | | | |

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.

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Costs/ patient / year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Nivolumab | | | | | |
| Initial treatment (week 1-16) | 240 mg | 240 mg | 2 x 120 mg | 8.0 | 16.0 x 120 mg |
| | or | | | | |
| | 480 mg | 480 mg | 4 x 120 mg | 4.0 | 16.0 x 120 mg |
| Follow-up treatment (from week 17) | 480 mg | 480 mg | 4 x 120 mg | 9.0 | 36.0 x 120 mg |
| Appropriate comparator therapy | | | | | |
| Monitoring wait-and-see approach | incalculable | | | | |



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Costs:

**Costs of the medicinal products:**

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of usage. 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.

| 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 | | | | | |
| Nivolumab 120 mg | 1 CIS | € 1,546.93 | € 1.77 | € 85.05 | € 1,460.11 |
| Appropriate comparator therapy | | | | | |
| Monitoring wait-and-see approach | incalculable | | | | |

LAUER-TAXE® last revised: 1 February 2022

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.

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.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the



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

## 3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

## 4. Process sequence

At its session on 25 May 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 24 August 2021, the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5, sentence 2 VerfO.

By letter dated 30 August 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient nivolumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 December 2021. The deadline for submitting written statements was 22 November 2021.

The oral hearing was held on 10 January 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 8 February 2022, and the proposed resolution was approved.

At its session on 17 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.



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**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal product | 25 May 2021 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 5 January 2022 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal product | 10 January 2022 | Conduct of the oral hearing, |
| Working group Section 35a | 19 January 2022<br>2 February 2022 | Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure |
| Subcommittee Medicinal product | 8 February 2022 | Concluding discussion of the draft resolution |
| Plenum | 17 February 2022 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 17 February 2022

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

Prof. Hecken



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