Gemeinsamer Bundesausschuss

Justification

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

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

Avelumab (New therapeutic indication: first-line maintenance treatment in adults with locally advanced or metastatic urothelial carcinoma)

of 19 August 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient avelumab (Bavencio) was listed for the first time on 1 October 2017 in the "LAUER-TAXE®", the extensive German registry of available medicinal products and their prices.

On 21 January 2021, Bavencio 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 18 February 2021, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company, on the approval of a new area of application, 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 avelumab with the new therapeutic indication (first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma). 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 June 2021, thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of avelumab 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, and the statements submitted in the written statement and oral hearing procedure, and the addenda 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 avelumab.

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 avelumab (Bavencio) in accordance with the product information

Bavencio is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy.

Therapeutic indication of the resolution (resolution of 19.08.2021):

see approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy; first-line maintenance treatment:

Appropriate comparator therapy:

Best supportive care

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

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

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 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 Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. Comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge.

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

on 1. Medicinal products containing the active ingredients cisplatin, doxorubicin, methotrexate, gemcitabine, vinflunine, pembrolizumab, atezolizumab and nivolumab are approved for the treatment of locally advanced or metastatic urothelial carcinoma.

on 2. Non-medicinal treatment is not considered.

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

- pembrolizumab (resolution of 16 March 2018, in the version as amended by the resolutions from 2 August 2018 and 20 June 2019),
- atezolizumab resolution of 16 March 2018, in the version as amended by the resolutions from 2 August 2018 and 20 June 2019),
- Nivolumab (resolution of 21 December 2017).

In addition, the following resolution on the commissioning of expert groups according to Section 35c paragraph 1 SGB V (expert groups off-label) is available:

- Carboplatin in combination with gemcitabine for the treatment of patients with unresectable locally advanced or metastatic urothelial carcinoma after failure of chemotherapy or when cisplatin therapy is not an option (19 April 2018).

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to § 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").

Accordingly, there are no recommendations in national or international guidelines, nor in scientific-medical societies' participation regarding maintenance treatment for

patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed under first-line platinum-based induction chemotherapy.

According to the current state of medical knowledge, no standard therapy has been established in this specific treatment situation. The G-BA assumes that patients in this situation receive patient-individual treatment to alleviate symptoms and improve their quality of life, particularly in view of the advanced stage of the disease. As a result, best supportive care is determined as the appropriate comparator therapy in the present therapeutic indication.

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

2.1.3 Extent and probability of the additional benefit

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

Adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy; first-line maintenance treatment:

Hint of a considerable additional benefit

Justification:

For the benefit assessment, the pharmaceutical company presents the results of the open-label randomised controlled trial JAVELIN Bladder 100 compared to Avelumab + Best supportive care (BSC) versus BSC.

The trial enrolled adults with unresectable, locally advanced or metastatic stage IV urothelial carcinoma who were progression-free after 4 to 6 cycles of first-line platinum-based chemotherapy. Patients were required to remain progression-free for a minimum of 4 and a maximum of 10 weeks after completion of first-line therapy and to have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) general condition of 0 or 1 at time of enrolment. Patients with brain metastases could be included in the study if the treatment of the metastases was completed and the metastases were stable.

A total of 700 patients were included in the study, randomised 1:1 to the intervention arm avelumab + BSC (N = 350) and the control arm BSC (N = 350). Randomisation was stratified by the degree of response to first-line platinum-based therapy (complete or partial response vs stable disease) and by the location of metastases (visceral vs non-visceral). In the study, two co-primary patient populations were considered, the population of PD-L1 positive patients and the overall population. The overall population is used for the benefit assessment, as avelumab is approved regardless of PD-L1 status.

In the study, avelumab was administered at a dose of 10 mg/kg body weight every 2 weeks, in deviation from the product information, which stipulates a dosage of 800 mg every 2 weeks regardless of body weight. For the comparison examined in the benefit assessment, it is assumed that the deviation from the dosage according to the product information has no relevant influence on the observed effects.

Patients receive the best supportive care in both the intervention and control arms. The BSC is implemented patient-individual and in accordance with local practice. Active tumour

therapies were not allowed, whereas palliative local radiotherapy of isolated lesions was allowed.

Treatment will continue in both study arms until disease progression, unacceptable toxicity, withdrawal of consent, or end of the study. Treatment with avelumab may, at the principal investigator and in consultation with the sponsor, continue after disease progression (even if treatment was discontinued in the interim) as long as patients continue to benefit from treatment.

The primary endpoint of the JAVELIN Bladder 100 study was overall survival. Patient-relevant secondary endpoints were endpoints regarding symptomatology, health status, and adverse events (AE).

For the JAVELIN Bladder 100 study, analyses are available for 2 data cut-offs:

- 1. Data cut-off (21.10.2019): planned interim analysis for the endpoint overall survival after 345 deaths in the overall population and 146 deaths in the population of PD-L1 positive patients,
- 2. Data cut-off (19.01.2020): 90-day safety update, which was subsequently submitted as part of the FDA marketing authorisation.

The pharmaceutical company bases its statements in the dossier exclusively on the results of the 1st data cut-off. Only updated data on overall survival for the 2. data cut-off and the pharmaceutical company provided adverse events. For the adverse events, it can be estimated that only a few additional events occurred between the 1st and the 2nd data cut-off. For the present benefit assessment, the results of the 1st data cut-off of 21.10.2019 are used, which is a planned interim analysis for the endpoint overall survival after 345 deaths in the overall population. The results of the 2nd data cut-off of 19.01.2020 on overall survival are presented additionally.

Extent and probability of the additional benefit

Mortality

The overall survival is defined in the JAVELIN Bladder 100 study as the time from randomisation to death from any cause.

For the endpoint overall survival, treatment with Avelumab + BSC showed a significant prolongation in overall survival compared to BSC.

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

Morbidity

Progression-free survival

Radiographic progression-free survival (PFS) was operationalised in the JAVELIN Bladder 100 study as the time to first documentation of disease progression or death regardless of the underlying cause of death. The occurrence of disease progression was assessed by imaging techniques and based on the RECIST criteria (version 1.1). The evaluation was conducted by a central, blinded, independent committee (BICR).

The result shows a statistically significant prolongation of PFS by treatment with avelumab+ BSC compared to BSC.

The endpoint component Mortality is already surveyed in the present study via the endpoint overall survival as an independent endpoint. The morbidity component assessment was not done symptom-related but exclusively utilising imaging (disease progression assessed by radiology according to the RECIST criteria).

Considering the aspects mentioned above, there are different views within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

Symptomatology (NFB1SI-18)

The "NCCN/FACT Bladder Symptom Index-18" (NFB1SI-18) is part of the FACT questionnaire system and asks about the symptomatology in patients with bladder cancer. The questionnaire consists of a total of 18 items for men and 17 items for women, respectively, which are divided into the 4 subscales "Disease-related Symptoms-Physical" (DRS-P), "Disease-related Symptoms-Emotional" (DRS-E), "Treatment Side Effects" (TSE) and "Function/Well-Being" (FWB). The DRS-P subscale contains 1 item that is only asked of men.

The two subscales, "Disease-related Symptoms-Physical" (DRS-P) and "Treatment Side Effects" (TSE), can be assigned to symptomatology.

"Disease-related Symptoms-Physical" (DRS-P) subscale:

In the dossier, the pharmaceutical company submits continuous evaluations based on a mixed-effect model repeat measurements (MMRM), taking into account the entire survey time point. The result shows no signs of statistically significant differences between the treatment groups.

"Treatment Side Effects" (TSE) subscale:

In the dossier, the pharmaceutical company submits continuous evaluations based on a mixed-effect model repeat measurements (MMRM), taking into account the entire survey time point. The result shows no signs of statistically significant differences between the treatment groups.

Health status (EQ-5D VAS)

In the JAVELIN Bladder 100 study, health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

In the dossier, the pharmaceutical company submits continuous evaluations based on a mixed-effect model repeat measurements (MMRM) taking into account the entire survey time point. The result shows no signs of statistically significant differences between the treatment groups.

Overall, there were no relevant differences in morbidity between the treatment groups.

Quality of life

To measure the quality of life, pharmaceutical companies present the "NCCN/FACT Bladder Symptom Index-18" (NFB1SI-18), which is inappropriate to represent the health-related quality of life. As no further instruments were collected in the JAVELIN Bladder 100 study to assess health-related quality of life, no suitable data on this endpoint category are available for the assessment of additional benefit.

Side effects

Adverse events

The results for the endpoint Total adverse events are only presented additionally.

In the JAVELIN Bladder 100 study, 98.3% of patients in the intervention arm and 78.8% of patients in the comparator arm experienced an adverse event.

Serious AE

There was no statistically significant difference in serious adverse events between the two treatment arms.

Severe AE (CTCAE grade ≥ 3)

There was a statistically significant difference between treatment arms in the time to severe adverse events with CTCAE grade ≥ 3 to the disadvantages of avelumab + BSC.

Discontinuation due to AE

No usable data are available for therapy discontinuation due to AE.

Specific AE

A detailed examination of the specific AEs shows a statistically significant disadvantage of avelumab + BSC for each of the specific AEs "Hypothyroidism" (PT, AE), "Gastrointestinal disorders" (SOC, AE), "Infections and infestations" (SOC, AE), "Arthralgia" (PT, AE), "Respiratory, thoracic and mediastinal disorders" (SOC, AE), "Skin and subcutaneous tissue disorders (SOC, AE)", "lipase elevated" (PT, severe AE), "amylase elevated" (PT, severe AE), "Metabolism and nutrition disorders" (SOC, severe AE). For the endpoint "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" (SOC, severe AE), there is a statistically

significant difference between the treatment groups to the benefit of avelumab + BSC compared to BSC.

No usable data are available for the endpoint "infusion-related reactions".

In its statements, the pharmaceutical company submitted evaluations for the endpoint "immune-mediated AEs" based on the a priori defined PT lists without any further causal stepwise exclusion linkage, separately for AEs, severe AEs and serious AEs. However, the overall rate of immune-mediated AEs is presented additionally, as there is no representation of the CTCAE grades of incoming PTs, which is necessary for the assessment of patient relevance, and therefore the proportion of events that are not patient-relevant is unclear. For the endpoint "immune-mediated SAE", there was no statistically significant difference between the treatment groups based on the subsequently submitted analyses. For the endpoint "immune-mediated severe AEs", there is a statistically significant difference between the treatment groups to the disadvantage of avelumab + BSC.

In the overall analysis of the endpoints on side effects, statistically significant disadvantages of avelumab are shown for the endpoint severe AEs and in detail predominantly for the specific AEs. Overall, a disadvantage for treatment with avelumab + BSC compared to BSC is noted in the area of adverse events.

Overall assessment

For the benefit assessment of avelumab as monotherapy in first-line maintenance treatment for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy, the pharmaceutical company presented results from the JAVELIN Bladder 100 study on the endpoint categories mortality, morbidity and side effects. In this study, avelumab + best supportive care was compared to best supportive care alone.

For the endpoint overall survival, there is a statistically significant advantage of avelumab, the extent of which is assessed as a significant improvement.

In the endpoint category morbidity, there are no differences relevant for the benefit assessment.

No suitable data are available with regard to health-related quality of life.

In the endpoint category side effects, there are overall disadvantages for avelumab in the severe AEs, and in detail predominantly also in the specific AEs.

The overall results show a significant improvement in overall survival. For disease symptomatology, there is neither an advantage nor a disadvantage for avelumab. No usable data on health-related quality of life are available. With regard to side effects, there are disadvantages in the case of severe AEs, as well as in detail predominantly in the case of specific AEs. However, the extent of these disadvantages is not judged to be so serious as to justify a downgrading in the overall assessment to the extent of additional benefit. Thus, a considerable additional benefit is found for avelumab + best supportive care compared to best supportive care alone.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the open-label, randomised, controlled phase III JAVELIN Bladder 100 study.

The risk of bias is rated as low for overall survival.

The risk of bias for the patient-reported endpoints symptomatology and health status is rated as high, firstly because of the lack of blinding and secondly because some patients were not included in the evaluation. For the endpoints concerning adverse events, no increased risk of bias is derived overall.

A relevant uncertainty in the overall statement on the additional benefit is, on the one hand, that no data are available on the quality of life, to which great importance is attached, especially in the palliative therapy situation in advanced disease. On the other hand, the clearly positive therapy effect on overall survival does not correspond to positive effects on the investigated disease symptomatology, which is pronounced in the present therapeutic indication of avelumab, also according to the relevant statements of the clinical experts in the written statement procedure, in the reality of care. In addition, a relatively small proportion of patients in the study received subsequent therapy with an immune checkpoint inhibitor compared to the current reality of care. These limitations lead to the reliability of data of the additional benefit being classified overall as "hint".

2.1.4 Summary of the assessment

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

"Bavencio is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy. "

For the benefit assessment, the pharmaceutical company submits the JAVELIN Bladder 100 study results, a randomised controlled trial with unblinded study treatment, in which avelumab in combination with best supportive care is compared against best supportive care.

For the endpoint overall survival, avelumab showed a statistically significant advantage, the magnitude of which was assessed as a significant improvement.

In the endpoint category morbidity, there are no differences relevant for the benefit assessment.

No suitable data are available with regard to health-related quality of life.

With regard to side effects, there are disadvantages in the case of severe AEs, as well as in detail predominantly in the case of specific AEs. However, the extent of these disadvantages is not judged to be so serious as to justify a downgrading in the overall assessment to the extent of additional benefit. Due to relevant uncertainties, the overall reliability of the additional benefit identified data is classified as "hint".

As a result, the G-BA found a hint of considerable additional benefit for avelumab compared with the appropriate comparator therapy.

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

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

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company. This figure is subject to uncertainty and should be regarded as an upper limit. The uncertainties are due in particular to the fact that a high proportion value was set for stage IV at the initial diagnosis. All patients with local recurrence were included in the target population. The implicit assumption was made that all patients with locally advanced or metastatic stage would receive chemotherapy.

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 Bavencio (active ingredient: avelumab) at the following publicly accessible link (last access: 27 May 2021):

https://www.ema.europa.eu/documents/product-information/bavencio-epar-product-information_de.pdf

Treatment with avelumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology and specialists in urology and participating in the Oncology Agreement who are experienced in the treatment of patients with urothelial carcinoma.

In accordance with EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient card. Patients are requested to carry the patient card with them at all times. The training material for health professionals and the patient card contain, in particular, instructions on how to deal with the immune-mediated side effects that can potentially occur with avelumab.

2.4 Treatment costs

The treatment costs are based on the product information as well as the information in the LAUER-TAXE® (last revised: 1 August 2021).

Suppose no maximum treatment duration is specified in the product information. In that case, 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.

Treatment duration:

Designation of the therapy	Treatment method	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Avelumab	Once every 14 days	26.1	1	26.1
Best supportive care	Patient-individual			
Appropriate comparator therapy				
Best supportive care	Patient-individual			

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Avelumab	800 mg	800 mg	4 x 200 mg	26.1	104.4 x 200 mg
Best supportive care	Patient-individual				
Appropriate comparator therapy					
Best supportive care	Patient-individual				

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 Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Cost after deduction of statutory rebates
Medicinal product to be assessed					
Avelumab	1 CIS	€ 834.55	€ 1.77	€ 45.59	€ 787.19
Best supportive care	Patient-individual				
Appropriate comparator therapy					
Best supportive care	Patient-individual				
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 August 2021

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 considered 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 standard expenditure in the course of the treatment are not shown.

According to the avelumab product information, patients are required to be premedicated with an antihistamine and paracetamol prior to the first 4 infusions of avelumab. The product information does not provide any specific information why the necessary costs cannot be quantified.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe)(Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 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 costs are not added to the pharmacy retail price but rather follow the rules for calculating in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

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 7 July 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 5 January 2021.

On 18 February 2021, the pharmaceutical company submitted a dossier for the benefit assessment of avelumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 18 February 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 avelumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 May 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 June 2021. The deadline for submitting written statements was 22 June 2021.

The oral hearing was held on 5 July 2021.

By letter dated 9 July 2021, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by IQWiG was submitted to the G-BA on 29 July 2021.

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 the 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 session of the subcommittee on 10 August 2021, and the proposed resolution was approved.

At its session on 19 August 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	7 July 2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	5 January 2021	New implementation of the appropriate comparator therapy
Working group Section 35a	29 June 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	5 July 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	14 July 2021 21 July 2021 4 August 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	10 August 2021	Concluding consultation of the draft resolution
Plenum	19 August 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 August 2021

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

Prof. Hecken