Justification

Gemeinsamer Bundesausschuss

to 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 (Reassessment after the Repeal of Orphan Drug Status (Metastatic Merkel Cell Carcinoma))

of 1 October 2020

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 proof 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 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 proof 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 medicinal product Bavencio® with the active ingredient avelumab was initially approved for the treatment of a rare disease (orphan drug) in accordance with Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999. This marketing authorisation as an orphan drug was granted for the following therapeutic indication: “Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC)”.

For this therapeutic indication, the G-BA decided on 16 March 2018 on the benefit assessment of avelumab on the basis of the statutory regulations on the benefit assessment of medicinal products for the treatment of a rare disease (Section 35a, paragraph 1, sentence 11 SGB V).

On 7 October 2019, the orphan designation of Bavencio® was withdrawn from the community register of medicinal products for the treatment of a rare disease. Consequently, its status as an orphan drug expired. As a result, the pharmaceutical company was requested by the G-BA in a letter dated 18 December 2019 to submit proof according to Chapter 5, Section 5, paragraphs 1 to 6 VerfO and to demonstrate the additional benefit compared with the appropriate comparator therapy.

On 6 March 2020, the pharmaceutical company submitted a dossier on the active ingredient avelumab in due time (i.e. within three months of receipt of the request of the G-BA) in corre-

sponding application of Section 35a paragraph 1 sentence 10 SGB V in conjunction with Chapter 5, Section 8, paragraph 1, number 6 and Section 12, number 2 of the Rules of Procedure (VerfO) of the G-BA.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 July 2020 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of 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. In order to determine the extent of the additional benefit, the G-BA has assessed 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 arrived at 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 treatment of adult patients with metastatic Merkel cell carcinoma (MCC).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with metastatic Merkel cell carcinoma (MCC); first-line treatment:

Therapy according to the doctor's instructions

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 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.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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. No medicinal therapies other than avelumab are approved for the treatment of metastatic Merkel cell carcinoma.

On 2. Non-medicinal treatment is not considered.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:
- Avelumab: Resolution of 16 March 2018

Section K of the Pharmaceuticals Directive Annex VI – Active ingredients that are prescribable in off-label use: Doxorubicin for metastatic Merkel cell carcinoma (resolution of 23 June 2011)

On 4. The generally accepted state of medical knowledge was illustrated by research for guidelines as well as systematic reviews of clinical studies in this indication.

The treatment options in this therapeutic indication are very limited. According to current guideline recommendations, patients with metastatic Merkel cell carcinoma should receive immunotherapy using PD-1/PD-L1 blockade. The guidelines specify the active ingredients avelumab, nivolumab and pembrolizumab for appropriate immunotherapy. For all three active ingredients, studies have shown a high response rate to immunotherapy in patients with metastatic Merkel cell carcinoma. However, these are only single-arm Phase II studies with few patients; this limits the reliability of data. The recommendations in the guidelines are therefore based on little evidence overall. The active ingredients nivolumab and pembrolizumab mentioned in the therapy recommendations are not approved for the treatment of metastatic Merkel cell carcinoma. There is thus a discrepancy between medicinal products authorised in the indication and those recommended in guidelines. There are no objective, patient-individual criteria that should be regularly taken into account when deciding between nivolumab and pembrolizumab. The G-BA therefore determines a therapy according to the doctor's instructions as an appropriate comparator therapy.

Because no medicinal therapies other than the avelumab under assessment are approved, the active ingredients pembrolizumab and nivolumab are considered to be equally suitable comparators in a clinical study.

According to the approved therapeutic indication, avelumab can be used independently of the therapy line. In care, patients with metastatic Merkel cell carcinoma are currently treated with an immuno-checkpoint inhibitor in the first line according to the recommendations of the guidelines. There is no recommendation or evidence for sequential treatment with different immuno-checkpoint inhibitors. Avelumab is therefore expected to be used in the first-line treatment of metastatic Merkel cell carcinoma. For the appropriate comparator therapy and thus for comparison in the benefit assessment, only the first-line treatment of metastatic Merkel cell carcinoma is addressed.

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

2.1.3 Extent and probability of the additional benefit

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

For the first-line treatment of adult patients with metastatic Merkel cell carcinoma an additional benefit is not proven.

Justification:

In order to prove an additional benefit of avelumab, the pharmaceutical company presents the pivotal JAVELIN Merkel 200 study. The JAVELIN Merkel 200 study is an ongoing, single-arm, open-label, multi-centre Phase II study.

The present study contains two parts; these differ in the characteristics of the patients included. Study part A included 88 patients who had already received at least one course of chemotherapy for the treatment of metastatic Merkel cell carcinoma. Study part B included 116 patients without prior systemic chemotherapy for the metastatic disease.

The study started in July 2014 and was conducted in Australia, France, Germany, Italy, Japan, Spain, and the US.

The pharmaceutical company submits the data cut-off of 2 May 2019 (15-month follow-up) for Study part A and the data cut-off of 14 September 2018 (36-month follow-up) for Study part B. In Study part A, the primary endpoint was the best overall response; in Study part B, it was the permanent response rate (lasting ≥ 6 months).

The single-arm JAVELIN Merkel 200 study is basically only suitable for comparing individual arms from different studies. For comparison with the appropriate comparator therapy, the pharmaceutical company identifies the single-arm KEYNOTE-017 study. Because of a lack of information on the study population, this study is not suitable for comparison and is excluded by the pharmaceutical company.

As a result, the pharmaceutical company was not able to provide appropriate comparative data to assess the additional benefit. It is not possible to assess the additional benefit based on this data basis. Thus, an additional benefit is not proven.

Taking into account the evidence on the medical benefit of avelumab, the severity of the disease, the lack of therapy alternatives with a proven benefit – with the exception of the provision in Annex VI of the Pharmaceuticals Directive – and the written statements of the medical professional associations on the current reality of care, avelumab may represent a relevant therapy option for adult patients with metastatic Merkel cell carcinoma (MCC).

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of the medicinal product Bavencio with the active ingredient avelumab. “Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC)”.

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

Therapy according to the doctor’s instructions (with selection of nivolumab and pembrolizumab)

For the assessment, the pharmaceutical company presents the still ongoing, single-arm, open, and multi-centre phase II study JAVELIN Merkel 200. Patients with metastatic Merkel cell carcinoma who had already received at least one course of chemotherapy and patients without prior systemic chemotherapy were included.

Because of the lack of suitable comparative data, the JAVELIN Merkel 200 study is not suitable for assessing the additional benefit of avelumab compared with the appropriate comparator

therapy. It is not possible to assess the additional benefit on this data basis. Thus, an additional benefit is not proven.

Avelumab may be a relevant therapy option for adult patients with metastatic Merkel cell carcinoma (MCC).

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

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

The resolution will be based on the information in the dossier of the pharmaceutical company. Because of the lack of up-to-date and transferable sources, the absolute survival rates and the proportion of patients who develop remote metastases during the course of the disease are questionable. Overall, the range of the SHI target population is 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 Bavencio® (active ingredient: avelumab) at the following publicly accessible link (last access: 19 June 2020):

https://www.ema.europa.eu/en/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, specialists in skin and venereal diseases, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with Merkel cell carcinoma.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on avelumab:

- Information brochure for patients
- Patient pass

The information material shall include, in particular, instructions on how to deal with the immune-mediated side effects potentially occurring with avelumab.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2020).

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 for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Avelumab	1 x every 14 days	26	1	26.1
Appropriate comparator therapy				
Therapy according to the doctor's instructions	different for each individual patient			

Usage and consumption:

Designation of the therapy	Dosage/application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/year	Average annual consumption by potency
Medicinal product to be assessed					
Avelumab	800 mg	800 mg	4 × 200 mg	26.1	104.4 × 200 mg
Appropriate comparator therapy					
Therapy according to the doctor's instructions	different for each individual patient				

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 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.

Costs of the medicinal product:

Designation of the therapy	Package 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					
Avelumab	1 CIS	€ 980.27	€ 1.77	€ 55.07	€ 923.43
Appropriate comparator therapy					
Therapy according to the doctor's instructions	different for each individual patient				
Abbreviations: CIS = Concentrate for the preparation of an infusion solution					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 August 2020

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

According to the product information of avelumab, before the first 4 infusions of avelumab, patients must be premedicated with an antihistamine and paracetamol. The product information does not provide any further details on this, which is why it is not possible to quantify the necessary costs.

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*) (status: 11th Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the production of parenteral preparations containing cytostatic agents of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use 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 sales 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 according to the regulations in Annex 3 of the *Hilfstaxe*.

3. Bureaucratic costs

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 28 January 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 27 March 2020, the pharmaceutical company submitted a dossier for benefit assessment to the G-BA in due time (i.e. within three months after receipt of the request of the G-BA) in corresponding application of Section 35a, paragraph 1, sentence 11 SGB V in conjunction with Chapter 5, Section 8, number 6 and Section 12, number 2 of the Rules of Procedure (VerfO) of the G-BA

By letter dated 30 March 2020 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 29 June 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2020. The deadline for submitting written statements was 22 July 2020.

The oral hearing was held on 10 August 2020.

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 session of the subcommittee on 22 September 2020, and the proposed resolution was approved.

At its session on 1 October 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	28 January 2020	Determination of the appropriate comparator therapy
Working group Section 35a	4 August 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	10 August 2020	Conduct of the oral hearing
Working group Section 35a	18 August 2020; 1 September 2020; 15 September 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	22 September 2020	Concluding discussion of the draft resolution
Plenum	1 October 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 1 October 2020

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

Prof. Hecken