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 Pembrolizumab (new therapeutic indication: Melanoma, ≥ 12 to <18 years of age)

of 19 January 2023

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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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

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

On 22 June 2022, Keytruda 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 European 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, 12.12.2008, p. 7).

On 18 July 2022, 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 pembrolizumab with the new

therapeutic indication "Keytruda as monotherapy is indicated for the treatment of adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma" 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 1 November 2022 on the G-BA website (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 pembrolizumab compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA 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 pembrolizumab.

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 Pembrolizumab (Keytruda) in accordance with the product information

Keytruda as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

Therapeutic indication of the resolution (resolution of 19.01.2023):

Keytruda as monotherapy is indicated for the treatment of adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma

Appropriate comparator therapy for pembrolizumab as monotherapy:

Therapy according to doctor's instructions

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

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

on 1. In addition to pembrolizumab as monotherapy for the treatment of advanced melanoma in adolescents aged 12 years and older, ipilimumab is approved for the treatment of advanced melanoma in adolescents aged 12 years and older.

In terms of authorisation status, medicinal products with the active ingredients ipilimumab, nivolumab, pembrolizumab, talimogene laherparepvec, dacarbazine and lomustine are available for adults for the treatment of advanced melanoma.

For patients whose melanoma has a BRAF V600 mutation, the combination therapies of encorafenib and binimetinib, cobimetinib and vemurafenib, dabrafenib and trametinib as well as the monotherapies dabrafenib, trametinib and vemurafenib are also approved.

on 2. The target population is assumed to be those patients for whom resection and/or radiotherapy with curative goals is unsuitable. In the present therapeutic indication, a non-medicinal treatment is therefore not considered.

on 3. For adolescents aged 12 years and older in the indication advanced melanoma, the following resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V is available:

- Ipilimumab: Resolution of 2 August 2018

For adults with the indication advanced melanoma, the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Vemurafenib: Resolution of 6 March 2014

- Pembrolizumab: Resolution of 4 February 2016
- Dabrafenib: Resolutions of 17 March 2016 and 16 June 2016 (3 April 2014)
- Trametinib: Resolution of 17 March 2016
- Ipilimumab: Resolutions of 7 April 2016 (2 August 2012), 7 April 2016 (5 June 2014), 2 August 2018 and 20 December 2018
- Cobimetinib: Resolution of 2 June 2016
- Nivolumab: Resolutions of 15 December 2016 (7 January 2016), 15 December 2016, 7 December 2017 and 20 December 2018
- Talimogene laherparepvec: Resolution of 15 December 2016
- Encorafenib: Resolution of 22 March 2019
- Binimetinib: Resolution of 22 March 2019

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 Section 35a SGB V".

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

There is little evidence on treatment options specifically for adolescents aged 12 years and older. The existing guidelines for the treatment of advanced (unresectable or metastatic) melanoma do not make any recommendations in this regard.

From the participation of the scientific-medical societies on the question of comparator therapy, a written statement is available from the Working Group for Dermatological Oncology (ADO) of the DKG (German Cancer Society), the German Dermatological Society (DDG) and the German Society for Haematology and Medical Oncology (DGHO). Accordingly, there is no separate standard for children and adolescents. The therapy of these few patients is oriented towards the therapy of adults. In this regard, the written statement mentions various systemic treatment options depending on BRAF V600 mutation status, which are based on the therapy recommendations for adults. Essentially, systemic treatment options include PD-1 antibodies ± ipilimumab or BRAF/MEK combination therapy.

With regard to the therapy of adults with advanced melanoma without BRAF V600 mutation, the present guidelines clearly recommend therapy with a PD-1 antibody.

These recommendations are in line with the results of the benefit assessments on PD-1 antibody monotherapies in adult therapy: For nivolumab, an indication of a major additional benefit was identified for non-pretreated adults with BRAF V600 wild-type tumour compared to dacarbazine (resolution of the G-BA of 7 January 2016). Similarly, in the benefit assessment of pembrolizumab for non-pretreated patients with BRAF

V600 wild-type tumour, a hint for a major additional benefit was identified compared to ipilimumab (resolution of the G-BA of 4 February 2016).

Monotherapy with ipilimumab has lost its value in non-pretreated adults due to its inferiority to PD-1 antibodies and is no longer recommended in the German S3 guideline. Ipilimumab as monotherapy has been approved since January 2018 for the treatment of adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma. Since the scientific-medical societies do not recommend ipilimumab monotherapy either, the G-BA does not consider this therapy option to be a suitable comparator, despite the existing marketing authorisation of ipilimumab for adolescents. Accordingly, ipilimumab is not determined to be an appropriate comparator therapy.

According to guidelines and the written statement of the scientific-medical societies, the combination therapy of nivolumab and ipilimumab is also an option for patients. However, the benefit assessment on nivolumab in combination with ipilimumab found a lower benefit compared to nivolumab (as monotherapy) for non-pretreated patients with BRAF V600 wild-type tumour (resolution of 20 December 2018). Against this background, the G-BA does not consider it appropriate to determine the combination therapy of nivolumab and ipilimumab in relation to the monotherapies with nivolumab or pembrolizumab as a suitable comparator in the context of therapy according to doctor's instructions.

For patients with a BRAF V600 mutation, specific treatment with BRAF or MEK inhibitors is also available and is unanimously recommended in the presence of this biomarker. According to the marketing authorisation, the combinations dabrafenib and trametinib, cobimetinib and vemurafenib as well as encorafenib and binimetinib are eligible.

In the benefit assessments of dabrafenib in combination with trametinib and cobimetinib in combination with vemurafenib, an indication of a major additional benefit was found for non-pretreated BRAF V600-mutated patients compared to vemurafenib monotherapy (resolutions of 17 March 2016 and 2 June 2016). In the outcome of the benefit assessment of encorafenib in combination with binimetinib, which was based on an adjusted, indirect comparison with the appropriate comparator therapy cobimetinib in combination with vemurafenib via the bridge comparator vemurafenib, an additional benefit for this patient population was not proven (resolution of 22 March 2019). Based on the clear recommendations in the guidelines and the written comments of the scientific-medical societies, it is nevertheless considered appropriate to also designate encorafenib in combination with binimetinib as an equally appropriate comparator therapy alongside dabrafenib in combination with trametinib and cobimetinib in combination with vemurafenib for patients with a BRAF V600 mutation. Due to the superiority of the combination of BRAF and MEK inhibitors, monotherapy with a BRAF inhibitor has lost importance and is therefore not determined as an appropriate comparator therapy.

The recommendations of the guidelines and the explanations of the scientific-medical societies for adults regarding treatment with PD-1 antibodies apply not only to patients with a BRAF V600 wild-type tumour but also to patients with a BRAF V600 mutation.

With regard to the benefit assessments of the PD-1 antibodies pembrolizumab and nivolumab, it should be noted that no data were available for non-pretreated patients with a BRAF V600 mutation compared to the appropriate comparator therapy, so that specifically for this patient group, in contrast to patients with BRAF V600 wild type, no additional benefit was determined. Against the background of the clear recommendations of the guidelines and scientific-medical societies, which name the PD-1 antibodies on an equal footing with the combinations of BRAF and MEK inhibitors, it is, however, considered appropriate to determine pembrolizumab and nivolumab as equally suitable appropriate comparator therapies for the first-line therapy of patients with BRAF V600 mutation in addition to the combination therapies consisting of BRAF and MEK inhibitors. The S3 guideline points out that there are no data on the best sequential therapy of BRAF/MEK inhibitors and checkpoint inhibitors.

Overall, for the treatment of adolescents aged 12 years and older, and taking into account the results from the corresponding benefit assessment procedures according to Section 35a SGB V for adults, the G-BA considers suitable comparators for a therapy according to the doctor's instructions within the framework of a clinical study:

- Vemurafenib + cobimetinib (only for patients with BRAF V600 mutation)
- Dabrafenib + trametinib (only for patients with BRAF V600 mutation)
- Encorafenib + binimetinib (only for patients with BRAF V600 mutation)
- Nivolumab

The therapies named as suitable comparators are not currently approved for the treatment of adolescents aged 12 years and older. There is a discrepancy between medicinal product approved in the indication and medicinal products used in health care.

However, the possibility of the off-label use of the active ingredients in a clinical study does not allow any conclusions to be drawn about their appropriateness in the off-label use in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V. This does not affect an off-label prescription in specific cases according to the criteria of the established case law of the Federal Social Court on off-label use not regulated in the Pharmaceuticals Directive.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

Adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma

An additional benefit is not proven.

Justification:

For adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma, the pharmaceutical company could not identify a randomised controlled trial for the direct comparison of pembrolizumab versus the appropriate comparator therapy.

Against this background, the pharmaceutical company identified the KEYNOTE 051 study to prove the additional benefit of pembrolizumab compared to the appropriate comparator therapy within the scope of an information search for further investigations.

The KEYNOTE 051 study is an open-label, ongoing, non-randomised, multicentre, 1-arm phase I/II study enrolling children and adolescents aged ≥ 6 months to < 18 years with various oncological diseases. A total of 161 patients were included in the study across all cohorts up to the data cut-off of 10.01.2020 evaluated in the dossier and decisive for the marketing authorisation. Of these, 9 patients have advanced melanoma, whereby 5 patients belong to the age group of 12 years and older considered here.

The adolescents were treated with 2 mg / kg body weight (BW) (maximum 200 mg) pembrolizumab in a cycle of three weeks. Treatment with pembrolizumab will be given for up to 24 months or until disease progression is confirmed by the principal investigator or until unacceptable toxicity occurs.

For the 5 patients, the pharmaceutical company submitted the results for the endpoints treatment response and adverse events in descriptive form. The pharmaceutical company describes that due to these few patients, a statement regarding the efficacy of pembrolizumab is not possible.

These descriptive data presented from the KEYNOTE 051 study are not suitable for deriving conclusions on the additional benefit of pembrolizumab in adolescents aged 12 years and older with advanced melanoma compared to the appropriate comparator therapy.

With regard to an evidence transfer from adult patients with advanced (unresectable or metastatic) melanoma to adolescents aged 12 years and older, the pharmaceutical company states that this cannot be carried out appropriately due to the requirement of the benefit assessment to provide a comparison with the appropriate comparator therapy, as no study with adult patients comparing pembrolizumab with the appropriate comparator therapy defined by the G-BA is known.

2.1.4 Summary of the assessment

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

"Keytruda as monotherapy is indicated for the treatment of adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma."

The G-BA determined the appropriate comparator therapy to be a therapy according to the doctor's instructions, which can be a treatment with specific BRAF or MEK inhibitors in the presence of a BRAF V600 mutation or a treatment with the immune checkpoint inhibitor nivolumab.

The pharmaceutical entrepreneur submitted individual data from the KEYNOTE 051 study, in which children and adolescents with various oncological diseases are treated with pembrolizumab. Of these, 9 patients have advanced melanoma, 5 of whom belong to the age group of 12 years and older considered here. For these 5 patients, results on treatment response and adverse events were provided in descriptive form by the pharmaceutical company. These data are not suitable for the proof of an additional benefit.

According to the pharmaceutical company, there is no suitable study on pembrolizumab versus the appropriate comparator therapy for an evidence transfer from adult patients with advanced (unresectable or metastatic) melanoma to adolescents aged 12 years and older. Overall, there are no adequate data to allow an assessment of the added benefit of pembrolizumab in adolescents aged 12 years and older with advanced melanoma compared with the appropriate comparator therapy. An additional benefit is not proven.

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

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

To estimate the possible number of patients, the pharmaceutical company carried out his own calculations based on the incidence rates of the Centre for Cancer Registry Data (ZfKD) and the population projection according to the Federal Statistical Office. On this basis, the pharmaceutical company indicated a number of one to four patients in the SHI target population. The information provided by the pharmaceutical company is subject to uncertainty due to the limited data basis on case numbers of advanced melanoma in adolescents aged 12 years and older, as most of the sources used refer to adults. Overall, it can be assumed that the number of patients is underestimated because the projected sample size for adolescents aged 12 to 17 years with melanoma is too low.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Keytruda (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 3 January 2023):

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

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with melanoma, as well as specialists in skin and sexually transmitted diseases, and specialists in paediatrics and adolescent medicine with specialisation in paediatric haematology and oncology, and other specialists participating in the Oncology Agreement.

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2023).

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 varies from patient to patient. 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 annual treatment costs shown refer to the first year of treatment.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Pembrolizumab	continuously, 1 x every 21 days	17.4	1	17.4
Appropriate comparator therapy				
Therapy according to doctor's instructions[2]	No data available			

Consumption:

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

The dosage of pembrolizumab in adolescents 12 years and older with melanoma is 2 mg per kg body weight, up to a maximum of 200 mg every 21 days.

For the calculation of the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. For body weight, a range between 47.1 kg for 12-year-olds and 67.0 kg for 17-year-olds is therefore assumed according to the official representative statistics "Microcensus 2017"[3].

[2] The medicinal product combinations vemurafenib + cobimetinib (only for patients with BRAF V600 mutation); dabrafenib + trametinib (only for patients with BRAF V600 mutation); encorafenib + binimetinib (only for patients with BRAF V600 mutation) and the active ingredient nivolumab are suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. All drug therapies that represent a suitable comparator for the present benefit assessment according to doctor's instructions are not approved in the present therapeutic indication for adolescents aged 12 years and older, which is why no costs are presented for these medicinal products.

[3] Information system of federal health reporting, average body measurements of the population (height in m, weight in kg). Characteristics of classification: Years, Germany, age, sex [online]. URL: https://www.gbe-bund.de/gbe/pkg_isgbe5.prc_menu_olap?p_uid=gast&p_aid=42472020&p_sprache=D&p_help=3&p_indnr=223&p_indsp=&p_ityp=H&p_fid=

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Pembrolizumab	2 mg/ KG BW = 94.2 mg 2 mg /kg = 134 mg	94.2 mg - 134 mg	1 x 100 mg- 2 x 100 mg	17.4	17.4 x 100 mg- 34.8 x 100 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions[2]	No data available				

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pembrolizumab 100 mg	1 CIS	€ 2,974.79	€ 1.77	€ 285.60	€ 2,687.42
Appropriate comparator therapy					
Therapy according to doctor's instructions[2]	No data available				
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 January 2023

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 € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Pembrolizumab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 12 October 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 18 July 2022, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 25 July 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 October 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2022. The deadline for submitting written statements was 22 November 2022.

The oral hearing was held on 5 December 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 10 January 2023, and the proposed resolution was approved.

At its session on 19 January 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee	12 October 2022	Determination of the appropriate comparator therapy

Medicinal product		
Working group Section 35a	29 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	5 December 2022	Conduct of the oral hearing
Working group Section 35a	13 December 2022 3 January 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	10 January 2023	Concluding discussion of the draft resolution
Plenum	19 January 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 January 2023

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

Prof. Hecken