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: small intestine cancer with MSI-H or dMMR, pretreated)

of 19 January 2023

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 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 11 November 2021, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for pembrolizumab, amongst other indications, in the indication "small intestine cancer with MSI-H or with dMMR and progression of the disease on or following at least one previous therapy" in accordance with Section 35a paragraph 5b SGB V. The pharmaceutical company expected marketing authorisation extensions for the active ingredient pembrolizumab within the period specified in Section 35a paragraph 5b SGB V for several therapeutic indications at different times.

In its session on 6 January 2022, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment

and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the last therapeutic indication of the therapeutic indications covered by the application, at the latest six months after the first relevant date. All marketing authorisations for the therapeutic indications covered by the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

For the present therapeutic indication "small intestine cancer with MSI-H or with dMMR and progression of the disease on or following at least one prior therapy", pembrolizumab received the extension of the marketing authorisation as a major type 2 variation as defined according to Annex 2 No. 2a to Regulation (EC) number 1234/2008 of the Commission from 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 25 April 2022. In accordance with the resolution of 6 January 2022, the benefit assessment of the active ingredient pembrolizumab in this new therapeutic indication thus began at the latest within four weeks, i.e., at the latest on 20 July 2022, after the last approval, which took place on 22 June 2022, of pembrolizumab in the therapeutic indications for the treatment of "melanoma in patients aged 12 years and older".

On 18 July 2022, the pharmaceutical company has submitted in due time a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new therapeutic indication "small intestine cancer with MSI-H or with dMMR and progression of the disease on or following at least one previous therapy".

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:

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

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 the following MSI-H or dMMR tumours in adults with:

- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Therapeutic indication of the resolution (resolution of 19.01.2023):

Keytruda as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- unresectable or metastatic small intestine cancer with disease progression on or following at least one prior therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with unresectable or metastatic small intestine cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least one prior therapy

Appropriate comparator therapy for pembrolizumab as monotherapy:

Therapy according to 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 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. Besides pembrolizumab, no other active ingredient is approved in the present therapeutic indication.

on 2. In the present therapeutic indication, a non-medicinal treatment is not considered.

on 3. No corresponding resolutions or assessments are available.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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

Against the background of the information in the European Public Assessment Report (EPAR)[2], the G-BA assumes that small intestine cancers with adenocarcinoma histology are exclusively addressed in the present therapeutic indication.

Additionally, it is assumed that there is no indication for curative treatment or that there is no primary or secondary resectability.

As a result of the systematic literature review, it can be stated that the evidence on treatment options in the present therapeutic indication is limited overall.

Against this background, the guideline of the National Comprehensive Cancer Network (NCCN) was additionally included in the evidence synopsis, as no higher-quality guidelines are available with regard to the methodology of guideline production. In addition, a clinical expert was interviewed about treatment options and the treatment standard of care in the reality of care. The main statements of the clinical expert are given in the following explanations.

According to the NCCN guideline, patients with pretreated adenocarcinoma of the small intestine with MSI-H/dMMR can be treated with the active ingredients or combinations of active ingredients 5-fluorouracil + folinic acid + irinotecan (FOLFIRI), nab-paclitaxel, pembrolizumab, nivolumab ± ipilimumab, as well as best supportive care alone. For patients who are not suitable for intensive therapy, the replacement of the treatment regimens FOLFIRI with irinotecan as monotherapy is recommended.

The clinical expert is also basically in favour of the use of the treatment regimen FOLFIRI in patients with pretreated unresectable or metastatic small intestine adenocarcinomas or in older patients for monotherapy with irinotecan. For unfit patients or patients who refuse further antineoplastic therapy, best supportive care is also an option, according to clinical experts.

There are no medicinal treatments approved for the treatment of small intestine adenocarcinoma other than pembrolizumab. There is a discrepancy between medicinal products approved in the indication and those used in healthcare/ recommended in guidelines.

[2] European Assessment Report (EPAR) Keytruda (Pembrolizumab); Committee for Medicinal Products for Human Use (CHMP); 24 March 2022, EMA/224161/2022; Procedure No. EMEA/H/C/003820/II/0109.

Overall, the G-BA considers the following treatment options to be suitable comparators within the framework of a clinical study for therapy according to the doctor's instructions:

- 5-fluorouracil + folinic acid + irinotecan (FOLFIRI),
- Irinotecan,
- Nab-paclitaxel,
- Nivolumab + ipilimumab
- and best supportive care alone.

Best Supportive Care (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

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.

A single-comparator study is usually not sufficient for the implementation of the therapy according to the doctor's instructions in a direct comparative study. It is expected that the investigators will be able to choose from several treatment options (multi-comparator study).

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:

An additional benefit is not proven.

Justification:

Data basis

For the benefit assessment, the pharmaceutical company submits the results of the pivotal study on pembrolizumab in the present therapeutic indication. This is the KEYNOTE 158 study, which included pretreated patients with advanced (metastatic and / or unresectable) solid tumours.

KEYNOTE 158

The KEYNOTE 158 study is a since February 2016 ongoing multicentre, open-label, single-arm phase II study.

The patients in the study will be treated with pembrolizumab according to the product information. For the benefit assessment, the pharmaceutical company forms a sub-population of patients with small intestine cancer and MSI-H from cohort K (any advanced tumour (except colorectal cancer) with MSI-H) (N = 27).

In addition to the primary endpoint objective response rate, endpoints of the categories mortality, morbidity, health-related quality of life and side effects were collected.

The study is being conducted in 55 study sites in Asia, Australia, Europe, North and South America.

Comparator data

The KEYNOTE 158 study is an uncontrolled study. Thus, this study does not include a comparator group which allows comparison of the results of treatment with pembrolizumab.

For the benefit assessment, the pharmaceutical company submits a comparison of individual arms of the studies KEYNOTE 158 and Zaanan 2011 (AGEO).

Study Zaanan 2011

The Zaanan 2011 study is a retrospective study of the Association des Gastroentérologues Oncologues (AGEO) study group. This study group had previously examined patient records of 93 patients with locally advanced or metastatic small intestine adenocarcinoma who had received first-line chemotherapy with 5-fluorouracil and folinic acid alone or in combination with irinotecan, cisplatin or oxaliplatin between November 1996 and February 2008. 51 of these patients received second-line chemotherapy. The Zaanan 2011 study examined those of these patients who had received 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) as second-line therapy. Information on the MSI-H or dMMR status of the study population is not available. The aim of the study was to assess the efficacy and tolerability of FOLFIRI as second-line therapy in patients with advanced small intestine adenocarcinoma. The pharmaceutical company uses the data of the total population with FOLFIRI therapy from the Zaanan 2011 study (N = 28) for the comparison of individual arms on the comparison side.

The study was conducted in 13 study sites in France.

Assessment:

The results from the KEYNOTE 158 study alone are not suitable for assessing the additional benefit of pembrolizumab as they do not allow a comparison with the appropriate comparator therapy.

MSI-H/dMMR tumour status

Pembrolizumab is approved for adults for the treatment of unresectable or metastatic small intestine cancer with MSI-H or dMMR and disease progression on or following at least one prior therapy.

Accordingly, the pharmaceutical company only considers cohort K from the KEYNOTE 158 study, which included patients with dMMR/MSI-H.

In the context of the study on the appropriate comparator therapy, the pharmaceutical company does not submit any information on the existence of the MSI-H/dMMR status.

The significance of the MSI-H/dMMR tumour status cannot be conclusively assessed according to the present state of medical knowledge.

Methodology of the comparison of individual arms of different studies

The pharmaceutical company presents a comparison of individual arms of the KEYNOTE 158 and Zaanan 2011 studies for the endpoints overall mortality and objective response rate. For the endpoints progression-free survival and severe adverse events, the pharmaceutical company compares the results of the two studies descriptively. The results on morbidity and health-related quality of life of the KEYNOTE 158 study are presented additionally.

The single-arm comparisons submitted by the pharmaceutical company are comparisons without a bridge comparator and without adjustment for potentially relevant effect modifiers or prognostic factors. These comparisons have inherent uncertainty due to the lack of randomisation and are not an adequate method of indirect comparison. Moreover, there are no effects for which it can be safely excluded in the present situation of a comparison of individual arms that they do not result solely from a systematic bias due to confounding variables.

Conclusion:

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of pembrolizumab as monotherapy in adult patients with unresectable or metastatic small intestine cancer with MSI-H or dMMR and disease progression on or following at least one previous therapy is not proven.

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 is approved as monotherapy for the treatment of unresectable or metastatic small intestine cancer with MSI-H or dMMR and disease progression on or following at least one prior therapy.

The appropriate comparator therapy was determined by G-BA to be a therapy according to doctor's instructions.

For the benefit assessment, the pharmaceutical company submitted the results from the KEYNOTE 158 study for the treatment with pembrolizumab. This is an uncontrolled study and therefore, does not include a comparator group.

For the assessment of the additional benefit, the pharmaceutical company submits a comparison of individual arms of the studies KEYNOTE 158 and Zaanan 2011.

These comparisons have inherent uncertainty due to the lack of randomisation and are not an adequate method of indirect comparison. Moreover, there are no effects for which it can be safely ruled out that they do not result solely from systematic bias.

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of pembrolizumab as monotherapy 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).

The resolution is based on the information from the dossier of the pharmaceutical company regarding the number of patients.

The range given by the pharmaceutical company is subject to uncertainty. The number of patients in the SHI target population could also lie outside this range. This is due in particular to the use of the 5-year prevalence as a baseline in conjunction with the proportion values transferred to it.

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 as well as specialists in internal medicine and gastroenterology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with small intestine cancer.

Before initiation of therapy with pembrolizumab, the presence of microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) should be confirmed by a validated test in a tumour sample.

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 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.

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
	or			
	continuously, 1 x every 42 days	8.7	1	8.7
Appropriate comparator therapy				
Therapy according to doctor's instructions[3]				
Best supportive care[4]	Different from patient to patient			

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.

[3] In addition to BSC, the following treatment options are also considered suitable comparators in a clinical study: 5-fluorouracil + folinic acid + irinotecan (FOLFIRI), irinotecan, nab-paclitaxel, nivolumab ± ipilimumab. However, the active ingredients mentioned are not approved in the therapeutic indication, which is why the costs are not presented.
[4] In the case of a comparison with best supportive care, also to be used additionally for the medicinal product to be assessed.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions[3]					
Best supportive care[4]	Different from patient to 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 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[3]					
Best supportive care[4]	Different from patient to patient				
Abbreviation: 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 23 March 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, number 2 VerfO.

By letter dated 26 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 27 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 Medicinal product	23 March 2021	Determination of the appropriate comparator therapy
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