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 Ivacaftor (Exceeding the € 50 Million Limit: Cystic Fibrosis, Patients from 18 Years of Age, R117H Mutation)

of 20 February 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 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 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 ivacaftor (Kalydeco®) was listed for the first time on 15 August 2012 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. Kalydeco® for the treatment of cystic fibrosis (CF) is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

In its session on 2 June 2016, the G-BA passed a resolution on the benefit assessment of ivacaftor in the therapeutic indication “Kalydeco is indicated for the treatment of patients aged 18 years and older with CF who have an R117H mutation in the CFTR gene” in accordance with Section 35a SGB V.

If the turnover of the orphan drugs with statutory health insurance at pharmacy sales prices as well as outside statutory medical care, including value added tax, exceeds € 50 million in the last twelve calendar months, the pharmaceutical company must, within three months of being requested to do so by the Federal Joint Committee, submit evidence in accordance with Section 5, paragraph 1 through 6 demonstrating the additional benefit compared with the appropriate comparator therapy.

The pharmaceutical company was informed about the exceeding of the € 50 million turnover limit by letter dated 22 March 2019 and was requested to submit a dossier for the benefit assessment in accordance with 35a SGB V. The pharmaceutical company submitted the final dossier to the G-BA in due time in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 6 VerfO on 28 August 2019.

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 2 December 2019, 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 ivacaftor 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 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 ivacaftor.

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 ivacaftor (Kalydeco®) in accordance with the product information

Kalydeco tablets are also indicated for the treatment of adults aged 18 years and older with cystic fibrosis (CF) who have an R117H mutation in the CFTR gene (see sections 4.4 and 5.1 of the product information).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients from the age of 18 years with cystic fibrosis who have an R117H mutation in the CFTR gene

- Best supportive care

Best supportive care (BSC) is defined as the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve the quality of life (especially antibiotics for pulmonary infections, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (in the sense of the Heilmittel-RL (Remedies Directive)), making full use of all possible dietary measures).

[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.

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.
3. As comparator therapy, medicinal products 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 other medicinal products are approved for the therapy of CF in adults with a R117H mutation.
The following medicinal products are approved for the symptomatic treatment of CF in adults: Aztreonam (Cayston®), carbocisteine, ceftazidim, ciprofloxacin, colistimethate, dornase alfa (Pulmozyme®), levofloxacin, meronem, mannitol (Bronchitol®), pancreatin, tobramycin.

On 2. In the treatment of CF, nutritional measures, support of the respiratory function, and physiotherapy (in the sense of the Remedies Directive) are generally considered as non-medicinal treatment.

On 3. For the group of patients to be considered in the present therapeutic indication “Patients from the age of 18 years with cystic fibrosis who have an R117H mutation in the CFTR gene”, the G-BA has passed the following resolution:
- Resolution on ivacaftor dated 2 June 2016 (*Orphan Drug* Status; is repealed with the present resolution)

On 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines and systematic reviews of clinical studies. For adult patients with R117H mutation, there is no specific standard therapy for this group of patients. The aforementioned medicinal and non-medicinal therapy options are available for symptomatic therapy. In the evidence provided, these are recommended for symptomatic therapy of CF, in particular, antibiotic therapy of pulmonary infections (ceftazidine, colistimethate, tobramycin), inhalation of medicinal products (mannitol, dornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin), and nutritional therapy and support of respiratory function (e.g. through physiotherapy). CF is thus treated individually for each patient to alleviate symptoms and improve the quality of life in the sense of BSC.

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 ivacaftor is assessed as follows:

Patients from the age of 18 years with cystic fibrosis who have an R117H mutation in the CFTR gene

Hint for a minor additional benefit.

Justification:

For the assessment of the additional benefit of ivacaftor in patients with cystic fibrosis who have an R117H mutation in the CFTR gene, the pharmaceutical company presented the pivotal, multi-centre, randomised, double-blind, placebo-controlled Phase III Study VX11-770-110 (hereinafter Study 110) in which ivacaftor + BSC was compared with placebo + BSC.

Included were 70 patients aged 6 years and older with an R117H mutation in at least one allele of the CFTR gene. As inclusion criteria for the definition of cystic fibrosis the following criteria had to be fulfilled: a chronic sinopulmonary disease and either a sweat chloride value ≥ 60 mmol/l or two cystic fibrosis-causing mutations. The sub-population of this study relevant for the present therapeutic indication (≥ 18 years) included 50 patients. Of these, 24 patients were randomised to the intervention arm (ivacaftor) and 26 patients to the comparator arm (placebo). The treatment with ivacaftor (150 mg every 12 hours according to the product information) or placebo was carried out in addition to the basic therapy. The study period of 24 weeks is considered an appropriate observation period for the present assessment.

From the data presented in the dossier, it appears that in the overall population of the study, patients received concomitant medication for the symptomatic treatment of cystic fibrosis, including dornase alfa, antibiotics, bronchodilators, corticosteroids, painkillers, vitamin preparations, and physiotherapy. However, according to the study protocol, the concomitant therapy was limited to inhaled hypertonic saline solution. This was not permitted within four weeks before the first intake of the study medication until shortly before the end of the study or had to discontinued before the start of study. Although a protocol change made the application possible retrospectively, only four patients of the relevant sub-population were included after this protocol change; for the majority of the patients examined, inhalation with hypertonic saline solution was not possible during the course of the study. The concomitant medication used in Study 110 therefore does not represent a complete implementation of the appropriate comparator therapy, best supportive care. In addition, there is a lack of information on the concomitant therapy of the relevant sub-population as well as whether and in how many patients the concomitant treatment was adjusted. This means that overall uncertainties have to be taken into account for the assessment of the additional benefit.

As a primary endpoint of the study, the “absolute change in FEV_1%” (percentage of forced expiratory one-second volume) was surveyed. In addition, endpoints in the categories mortality, morbidity, quality of life, and side effects were surveyed. All endpoints were surveyed up to a maximum of four weeks after the end of treatment.

Extent and probability of the additional benefit

Mortality

No deaths occurred in Study 110.

Morbidity

Forced expiratory volume per second (FEV$_1$ %)

The forced expiratory volume per second (FEV$_1$), which is represented as a percentage of the forced expiratory volume per second of standardised normal value as FEV$_1$ %, was measured as an absolute change. In Study 110, a statistically significant difference for the FEV$_1$% in favour of IVA + BSC compared with placebo + BSC was determined.

Different opinions on patient relevance to FEV$_1$% exist. The overall statement on the extent of the additional benefit remains unaffected.

Body Mass Index (BMI)

The BMI is used to assess body weight in relation to height. In the present therapeutic indication, indications for malnutrition may be derived. However, for the endpoint absolute change in BMI, Study 110 did not show a statistically significant difference between the treatment groups. In addition, the patients included in the studies already had a BMI in the normal range at the start of the studies. Statements on additional benefit cannot be derived from this.

Pulmonary exacerbations

Pulmonary exacerbations, above all those that lead to admission to hospital, represent a clinically relevant endpoint and are considered patient-relevant.

For the endpoints pulmonary exacerbations and hospitalisations because of pulmonary exacerbations, no statistically significant differences between IVA + BSC and placebo +BSC were shown.

The endpoint i.v. antibiotics therapy caused by pulmonary exacerbations does not allow any further statements (for example: on severe exacerbations) since the i.v. administration is also dependent on the pathogen spectrum and not solely correlated to the degree of severity of the pulmonary exacerbation.

Symptomatology measured through the Cystic Fibrosis Questionnaire-Revised (CFQ-R)

The endpoint symptomatology was assessed using the disease-specific CFQ-R (patient version) and included the domains respiratory system and weight problems as well as gastrointestinal symptoms. The CFQ-R is a validated questionnaire that measures the subjective perception through the patient's eye ("patient-reported outcome, PRO").

For the domain respiratory system, a statistically significant advantage of the mean difference between IVA + BSC and placebo + BSC was found for the patient version of the CFQ-R. In order to assess the relevance of the result, the standardised mean difference in the form of the Hedges' g is considered. Its 95% confidence interval lies completely outside the irrelevance range of −0.2 to 0.2. A relevant effect can thus be assumed. For the morbidity endpoint symptomatology of the respiratory system (surveyed via CFQ-R), there is thus a relevant advantage for ivacaftor. For the domains gastrointestinal symptoms and weight problems, there was no statistically significant difference between the treatment groups.

Sweat chloride concentration (mmol/l)

The measurement of chloride values in sweat is used as a standard diagnostic procedure because the values reflect the functionality of the CFTR protein, which is the pathophysiological cause of the disease. Because the extent of a reduction in sweat chloride concentration is not directly associated with the extent of the change in symptomatology, the

endpoint is not considered to be directly relevant to patients and is considered complementary.

In Study 110, the endpoint sweat chloride concentration was surveyed as an absolute change at week 24. Study 110 showed a statistically significant advantage of IVA + BSC compared with placebo + BSC for the absolute change in the sweat chloride concentration.

Quality of life

Health-related quality of life measured through CFQ-R

The quality of life was recorded using the validated, disease-specific instrument CFQ-R (patient version). Of these, the domains of physical well-being, emotional state, vitality, social limitations, role function, body image, eating disorders, burden of therapy, and subjective perception of health are to be assigned to health-related quality of life. For each of the domains mentioned, evaluations of the changes observed over the course of the study (mean value difference) are available.

Statistically significant differences of IVA + BSC compared with placebo + BSC arise in the domains of physical well-being, emotional state, vitality, social limitations, and eating disorders. In all cases there are differences in favour of ivacaftor. In order to assess the relevance of the results, the standardised mean difference in the form of the Hedges' g is considered. Its 95% confidence interval lies completely outside the irrelevance range of −0.2 to 0.2 in the domains emotional state and vitality. A relevant effect can thus be assumed for these domains. Effect modifications exist in the domain emotional state for the characteristic "*Pseudomonas aeruginosa* infection status" as well as for the domains vitality and social limitations for the characteristic "sex". Because these effect modifications only show up in individual quality-of-life endpoints, and a medical rationale – especially for endpoints of the category quality of life – is missing, the entire relevant population is considered. Overall, there is a relevant advantage for ivacaftor in the quality of life category for the endpoints emotional state and vitality (measured by CFQ-R).

Side effects

No statistically significant differences were observed for the endpoints AE, SAE, and therapy discontinuations because of AE.

In the specific AEs, a statistically significant disadvantage of IVA + BSC compared with placebo + BSC was found for the endpoint oropharyngeal pain (preferred term).

Overall assessment

For the benefit assessment of ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 18 years and older who have an R117H mutation in the CFTR gene, the direct comparison between IVA + BSC and placebo + BSC of Study 110 was used. Results on mortality, morbidity, quality of life, and side effects are obtained.

No deaths occurred in Study 110.

In the morbidity category, a statistically significant effect in favour of ivacaftor was found for the endpoint respiratory system symptomatology (measured via CFQ-R); this was assessed as clinically relevant. For the other morbidity endpoints relevant for the assessment (pulmonary exacerbations, gastrointestinal symptoms, and weight problems) no relevant effects were found.

In the quality of life category, there are statistically significant advantages in the domains of emotional state and vitality of the CFQ-R questionnaire. These are assessed as clinically relevant.

In the side effects category, there are no statistically significant differences in the overall rates of adverse events, serious adverse events, and therapy discontinuation because of adverse events.

The advantages in the symptomatology of the respiratory system as well as in the quality-of-life endpoints of emotional state and vitality result in an additional benefit for ivacaftor compared with the appropriate comparator therapy BSC.

Overall, the G-BA classifies the extent of the additional benefit of ivacaftor as minor based on the criteria in Section 5, paragraph 7 of the AM-NutzenV, taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. In particular, no positive effects on serious symptoms such as pulmonary exacerbations have been observed. The benefits observed are thus not considered sufficient for a considerable additional benefit.

Reliability of data (probability of additional benefit)

The reliability of data is limited, in particular because of the incomplete implementation of the appropriate comparator therapy, best supportive care. For the majority of the patients examined, inhalation with hypertonic saline solution was not possible in the course of the study, although this is usually a relevant part of the standard therapy in the context of care. In addition, there is a lack of information on the concomitant therapy of the relevant sub-population as well as whether and in how many patients the concomitant treatment was adjusted.

In the overall view, these uncertainties regarding the reliability of data result in a hint for an additional benefit.

2.1.4 Summary of the assessment

The present assessments is a renewed benefit assessment of the orphan drug Kalydeco® with the active ingredient ivacaftor after the € 50 million turnover limit was exceeded. Ivacaftor is used for the treatment of cystic fibrosis. The present assessment refers exclusively to adult patients (> 18 years) who have an R117H mutation in the CFTR gene.

Ivacaftor has received marketing authorisation as an orphan drug.

Best supportive care (BSC) was determined as an appropriate comparator therapy by the G-BA.

The pharmaceutical company presented the results of Study VX11-770-110 in which ivacaftor + BSC was compared with placebo + BSC. In total, 50 patients were included. The treatment lasted 24 weeks.

A statistically significant and relevant benefit of ivacaftor was observed for the morbidity endpoint respiratory system symptomatology, which was assessed by the *Cystic Fibrosis Questionnaire-Revised* (CFQ-R)- questionnaire.

In addition, statistically significant and relevant benefits of ivacaftor were observed for the health-related quality of life endpoints emotional state and vitality (also measured by CFQ-R).

In terms of overall survival as well as in the category side effects (overall rates of adverse events, serious adverse events, and therapy discontinuation because of adverse events), no relevant differences between treatment groups were found.

The extent of the additional benefit based on the effects mentioned above is rated as minor, especially since no positive effects on serious symptoms such as pulmonary exacerbations are observed.

The reliability of data is limited because of the incomplete implementation of the appropriate comparator therapy, best supportive care. In particular, inhalation with hypertonic saline solution was not possible for the majority of the patients examined during the course of the study.

In the overall view, for adult patients (> 18 years) in whom there is an R117H mutation in the CFTR gene, there is a hint for a minor additional benefit of ivacaftor compared with BSC.

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

The G-BA uses the following derivation of patient numbers in order to enable a consistent examination of patient numbers, taking into account the most recent resolution (15 August 2019) on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication of cystic fibrosis:

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

A total patient group of currently approx. 8000 patients with cystic fibrosis in Germany is assumed. [2]

This figure differs from the calculation in the dossier by the pharmaceutical company, which assumes a total population of 6106 patients with cystic fibrosis. However, this figure is subject to uncertainties and represents an underestimate because patients without process data and up-to-date consent forms were not taken into account. Furthermore, there is currently no indication that the number of patients in the overall collective has changed significantly since the 2012 report (8042 patients ever reported and still alive at that time). This number has already been adjusted to eliminate multiple responses in accordance with the information in the documentation).

For this purpose, the G-BA takes into account the patient numbers of the resolution according to Section 35a SGB V of 2 June 2016 in the same therapeutic indication (approx. 35–44 patients).

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 Kalydeco® (active ingredient: ivacaftor) at the following publicly accessible link (last access: 5 February 2020):

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

Treatment with ivacaftor should only be initiated and monitored by specialists who are experienced in the treatment of patients with cystic fibrosis.

[2] https://www.muko.info/ (https://www.muko.info/englisch-version/) Website of Mukoviszidose e.V. (German Cystic Fibrosis Association) [accessed 27 June 2019]

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2020).

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 130 a 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.

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

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 therapy 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 indicated in the product information.

The patients in this therapeutic indication receive best supportive care. The treatment costs for best supportive care are different for each individual patient.

Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed.

The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

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				
Ivacaftor	continuously, 2 × daily	365	1	365
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Best supportive care	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					
Ivacaftor	150 mg	300 mg	2 × 150 mg	365	730 × 150 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				

Costs:

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					
Ivacaftor 150 mg	56 FCT	€ 16,432.12	€ 1.77	€ 937.86	€ 15,492.49
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				
Abbreviations: FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 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 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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for

additionally required SHI services had to be taken into account.

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 June 2019.

On 28 August 2019, the pharmaceutical company submitted a dossier for the benefit assessment of ivacaftor to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, Number 6 VerfO.

By letter dated 28 June 2019 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 ivacaftor.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 December 2019. The deadline for submitting written statements was 23 December 2019.

The oral hearing was held on 7 January 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 11 February 2020, and the proposed resolution was approved.

At its session on 20 February 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	12 June 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal Products	7 January 2020	Conduct of the oral hearing
Working group Section 35a	14 January 2020 4 February 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure

Subcommittee Medicinal Products	11 February 2020	Concluding discussion of the draft resolution
Plenum	20 February 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 February 2020

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

Prof. Hecken