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 (New Therapeutic Indication: Cystic Fibrosis, Combination Therapy with Ivacaftor/Tezacaftor/Elexacaftor in Patients 12 Years and Older (Heterozygous for F508del and MF Mutation))

of 18 February 2021

Contents

1. Legal basis

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

On 21 August 2020, ivacaftor received the marketing authorisation for a new therapeutic indication classified as a major type 2 variation according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of a marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 26 August 2020, the pharmaceutical company 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 ivacaftor with the new therapeutic indication (cystic fibrosis, combination therapy with ivacaftor/tezacaftor/elexacaftor for patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have a mutation with minimal function on the second allele) 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 December 2020 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of 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 written statements submitted in the written and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative) according to 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 light of the above and taking into account the written 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 indicated in a combination regimen with ivacaftor /tezacaftor /elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508del mutation in the CFTR gene or heterozygous for F508del and have a minimal function (MF) mutation in the CFTR gene.

Therapeutic indication of the resolution (resolution of 18 February 2021):

Kalydeco tablets are used in the framework of a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are heterozygous for F508del and have a minimal function (MF) mutation in the CFTR gene.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene as well as a mutation with minimal function (MF) on the second allele

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-Richtlinie (Remedies Directive)), making full use of all possible dietary measures).

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

[1] General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

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

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

On 1. The following medicinal products are approved for symptomatic therapy of CF:

Aztreonam, carbocisteine[2], ceftazidim, ciprofloxacin, colistimethate, dornase alfa, levofloxacin[3], meronem, mannitol, 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 patient group to be considered in the present therapeutic indication “Patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene as well as a mutation with minimal function (MF) on the second allele”, there are no resolutions.

On 4. The generally accepted state of medical knowledge was illustrated by research for guidelines as well as systematic reviews of clinical studies in the present indication. For patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene as well as a mutation with minimal function (MF) on the second allele, there are no approved specific treatment options. As stated above, only best supportive care (BSC) is considered for these patients and is determined as the appropriate comparator therapy. 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 Remedies Directive), making full use of all possible dietary measures).

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

[2]Approved for adolescents from the age of 13 years and adults with CF

[3]Approved only for adult patients with CF

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor (IVA/TEZ/ELX + IVA) is assessed as follows:

Patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene as well as a mutation with minimal function (MF) on the second allele

There is a hint for a major additional benefit

Justification:

For the assessment of the additional benefit of IVA/TEZ/ELX + IVA in patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene as well as a mutation with minimal function (MF) on the second allele, a multi-centre, randomised, double-blind, placebo-controlled Phase III study VX17-445-102 (hereinafter referred to as Study 102) was submitted by the pharmaceutical company.

Patients had to have a forced expiratory volume in one second (FEV1) of ≥ 40% and ≤ 90% of the standardised normal value for age, sex, and height at the time of screening. Patients with acute upper or lower respiratory tract infection or infection of the lungs with organisms associated with a more rapid decrease in pulmonary status were excluded. A total of 405 patients were included in the study; they were randomised in a 1:1 ratio to either treatment with IVA/TEZ/ELX + IVA + BSC (N = 201) or placebo + BSC (N = 204). Stratification factors were age (< 18 years / ≥ 18 years), sex (male / female), and FEV1 as a percentage of the standardised normal value (< 70% / ≥ 70%).

The treatment phase was 24 weeks.

Mortality

No deaths occurred in Study 102.

Morbidity

Pulmonary exacerbations

Pulmonary exacerbations, above all those that lead to admission to hospital, present a clinically relevant endpoint and are to be viewed as patient-relevant.

For pulmonary exacerbations, there is a statistically significant difference to the advantage of IVA/TEZ/ELX + IVA + BSC compared with placebo + BSC.

Hospitalisation because of pulmonary exacerbations

For hospitalisation because of pulmonary exacerbations, there is a statistically significant difference to the advantage of IVA/TEZ/ELX + IVA + BSC compared with placebo + BSC.

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 the gastrointestinal domain. The CFQ-R is a questionnaire that measures the subjective perception of patients (“patient-reported outcome”, PRO) and their assessment by parents/caregivers.

In accordance with to the current methodological procedure of IQWiG (Methods paper 6.0 published on 5 November 20201), for patient-reported endpoints, the IQWiG considers a responder threshold for responder analysis of at least 15% of the scale range of an instrument (in the case of analyses conducted post hoc, of exactly 15% of the scale range) to be necessary in order to reliably reflect a change that is noticeable for patients. Within the framework of the written statement procedure, the pharmaceutical company submitted responder analyses with a responder threshold of 15% of the scale range for all patient-reported endpoints.

For the domains respiratory system and weight problems, the responder analysis (improvement of at least 15 points) shows a statistically significant difference to the advantage of IVA/TEZ/ELX + IVA + BSC compared with placebo + BSC.

For the domain gastrointestinal symptoms, the responder analysis (improvement of at least 15 points) showed no statistically significant difference between the treatment groups.

Body Mass Index (BMI) and BMI z-score

The BMI is used to assess body weight in relation to height. In the present indication, body weight or BMI is important because developmental disorders and disturbed nutrient uptake are among the typical signs of cystic fibrosis. This endpoint is considered to be a patient-relevant morbidity parameter, especially in children with characteristic, disease-related growth disorders. Data adjusted for age and sex (z-scores) are preferred over absolute values.

For the endpoint absolute change in BMI as well as the change in BMI z-score, Study 102 showed a statistically significant difference to the advantage of IVA/TEZ/ELX + IVA + BSC compared with placebo + BSC. However, the relevance of this magnitude cannot be conclusively assessed because the patients included in both treatment groups already had a BMI in the normal range at baseline.

Forced one-second volume (FEV1)

Forced one-second volume (FEV1), presented as the percentage of forced one-second volume relative to the standardised normal value as FEV1%, was measured as absolute change over 24 weeks of treatment in Study 102. Here, there is a statistically significant difference to the advantage of IVA/TEZ/ELX + IVA + BSC compared with placebo + BSC.

There are different opinions on the patient relevance of FEV1%. The overall statement on the extent of the additional benefit remains unaffected.

Sweat chloride concentration (mmol/l)

The determination of the chloride concentration in sweat is used as a standard diagnostic procedure because the values reflect the functionality of the CFTR protein, whereby the disease is pathophysiologically determined. 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 102, the endpoint sweat chloride concentration was surveyed as an absolute change at Week 24. There is a statistically significant difference for the absolute change in sweat chloride concentration in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC compared with placebo + BSC.

Quality of life

Health-related quality of life measured through CFQ-R

Quality of life was assessed by the validated, disease-specific quality of life instrument CFQ-R using the patient version and included the domains of physical well-being, emotional state, vitality, social limitations, role functioning, body image, eating disorders, burden of therapy, and subjective health assessment.

Here, too, within the framework of the written statement procedure, the pharmaceutical company submits responder analyses with a response threshold of 15% of the scale range for all patient-reported endpoints.

For all domains of the health-related quality of life category of the CFQ-R (physical well-being, emotional state, vitality, social limitations, role functioning, body image, eating disorders, burden of therapy, and subjective health assessment), the responder analysis (improvement by at least 15 points) showed statistically significant differences to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC compared with placebo + BSC.

Side effects

For the results on the overall rate of adverse events (AE), there are data on the effect estimate.

For the endpoints SAEs and discontinuation because of AEs, there were no statistically significant differences between the treatment groups.

In the category side effects, there was no statistically significant difference between the treatment arms of the study in the overall view.

Overall assessment

For the benefit assessment of IVA/TEZ/ELX + IVA in patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene as well as a mutation with minimal function (MF) on the second allele, a multi-centre, randomised, double-blind, placebo-controlled Phase III study VX17-445-102 (hereinafter referred to as Study 102) was submitted by the pharmaceutical company. The direct comparison yields results on mortality, morbidity, quality of life, and side effects.

No deaths occurred in Study **102**.

In the morbidity category, for the endpoints pulmonary exacerbations and hospitalisation because of pulmonary exacerbations and in the respiratory system and weight problems domains of the CFQ-R, there was a statistically significant difference to the advantage of IVA/TEZ/ELX + IVA + BSC compared with placebo + BSC.
For the domain gastrointestinal symptoms of the CFQ-R, there was no statistically significant difference between the treatment groups. The synopsis of the results on morbidity showed a difference relevant for the benefit assessment in favour of IVA/TEZ/ELX + IVA + BSC compared with placebo + BSC.

In the category of quality of life, all domains of the CFQ-R (physical well-being, emotional state, vitality, social limitations, role functioning, body image, eating disorders, burden of therapy, and subjective health assessment) showed statistically significant differences to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC compared with placebo + BSC. The synopsis of the results on health-related quality of life showed a difference relevant for the benefit assessment in favour of IVA/TEZ/ELX + IVA + BSC compared with placebo + BSC.

In the overall view, in the categories mortality and side effects, there were no statistically significant differences between the treatment groups.

In summary, for patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene and have a minimal function (MF) mutation, there is a major additional benefit of IVA/TEZ/ELX + IVA compared with the appropriate comparator therapy BSC.

Reliability of data (probability of additional benefit)

This assessment is based on the results of the Study 102 on patients aged 12 years and older with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and have a mutation with minimal function on the second allele.

For the present benefit assessment, it remains unclear whether the concomitant therapy used in Study 102 represents a full implementation of the appropriate comparator therapy BSC. This estimate results from the fact that data on therapy adjustment in the sense of a dose increase or increase in the frequency of symptomatic therapy in the course of the study are lacking. The reliability of the study results for the present research question is therefore limited. Based on Study 102, at most, hints for determining the additional benefit can be derived for all endpoints presented.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor (IVA/TEZ/ELX + IVA). Ivacaftor (trade name: Kalydeco) was approved as an orphan drug, but has exceeded the € 50 million turnover limit.

The present resolution relates to the therapeutic indication “in the framework of a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are heterozygous for F508del and have a minimal function (MF) mutation in the CFTR gene”.

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

For the assessment of the additional benefit, the pharmaceutical company presented a multi-centre, randomised, double-blind, placebo-controlled phase III study VX17-445-102 in which the administration of IVA/TEZ/ELX + IVA compared with placebo, in each case in addition to the basic therapy for the treatment of cystic fibrosis, was investigated in patients in the present therapeutic indication for a duration of 24 weeks.

In the overall view of the results of the study, there is a statistically significant difference in favour of IVA/TEZ/ELX + IVA in the endpoints pulmonary exacerbations and hospitalisation because of pulmonary exacerbations as well as in the domains of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) in the categories morbidity (respiratory system and weight problems) and all domains of the category quality of life (physical well-being, emotional state, vitality, social limitations, role functioning, body image, eating disorders, burden of therapy, and subjective health assessment).

For the endpoints of mortality and side effects as well as the gastrointestinal symptoms domain of the CFQ-R, there were no statistically relevant differences between the treatment groups.

In summary, for patients aged 12 years and older with cystic fibrosis who are heterozygous for a F508del mutation in the CFTR gene and have a minimal function (MF) mutation, there is a hint for a major additional benefit of IVA/TEZ/ELX + IVA compared with the appropriate comparator therapy 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 (17 December 2020) 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[4].

This figure differs from the calculation in the dossier by the pharmaceutical company, which assumes a total population of 6340 patients with cystic fibrosis. However, this figure is subject to uncertainties and is underestimated because patients without event history 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).

The number of 1002 patients in the SHI target population calculated by the pharmaceutical company is an underestimate, especially in the overall view.

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: 9 February 2021):

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

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

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 2021).

For the cost representation, only the dosages of the general case are considered. If the treatment duration is unlimited, initial induction regimens are to be disregarded in the representation of costs. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

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.

[4] Mukoviszidose e.V. - Bundesverband Cystische Fibrose (CF) Webseite Mukoviszidose e.V.

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

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, 1 × daily	365	1	365
Ivacaftor/tezacaftor/ elexacaftor	continuously, 1 × 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	150 mg	1 × 150 mg	365	365 × 150 mg
Ivacaftor/tezacaftor/elexacaftor	150 mg/100 mg/200 mg	150 mg/100 mg/200 mg	2 × 75 mg/50 mg/100 mg	365	730 × 75 mg/50 mg/100 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated based on the rebates according to 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 based on consumption. Having determined the number of packs of a particular potency, the

costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Ivacaftor 150 mg	56 FCT	€ 16,432.12	€ 1.77	€ 937.86	€ 15,492.49
Ivacaftor/tezacaftor/elexacaftor 75 mg/50 mg/100 mg	56 FCT	€ 12,867.29	€ 1.77	€ 734.27	€ 12,131.25
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 selling price (LAUER-TAXE®) as last revised: 1 February 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

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

At its session on 25 February 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 26 August 2020, 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 2.

By letter dated 1 September 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient ivacaftor.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 November 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 December 2020. The deadline for submitting written statements was 22 December 2020.

The oral hearing was held on 11 January 2021.

By letter dated 12 January 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by the IQWiG was submitted to the G-BA on 28 January 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and 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 9 February 2021, and the proposed resolution was approved.

At its session on 18 February 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	25 February 2020	Determination of the appropriate comparator therapy
Working group Section 35a	6 January 2021	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	11 January 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 January 2021 2 February 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	9 February 2021	Concluding discussion of the draft resolution
Plenum	18 February 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 18 February 2021

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

Prof. Hecken