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 Ivacaftor (new therapeutic indication: cystic fibrosis, combination regimen with Ivacaftor/ Tezacaftor/ Elexacaftor, 6 to 11 years (heterozygous for F508del and MF mutation))

of 4 August 2022

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 is 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 is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

Within the previously approved therapeutic indications, the sales volume of ivacaftor with the statutory health insurance at pharmacy sales price including value-added tax exceeded € 50 million. Evidence must therefore be provided for ivacaftor in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 7 January 2022, Kalydeco received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 3 February 2022, i.e. no later than four weeks after the pharmaceutical company has been notified of the authorisation for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time 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 (treatment of patients aged 6 to 11 years with CF, who are heterozygous for the F508del mutation in the CTFR gene and show an MF mutation on the second allele (patients with F508del/ MF mutation).

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 16 May 2022, 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, 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 come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of 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, adolescents and children aged 6 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene.

Therapeutic indication of the resolution (resolution of 4 August 2022):

Kalydeco is indicated in a combination regimen with ivacaftor/ tezacaftor/ elexacaftor for the treatment of children aged 6 to 11 years with cystic fibrosis, who are heterozygous for an F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Children aged 6 to 11 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele

Appropriate comparator therapy for ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor:

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 (in particular antibiotics for pulmonary infections, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (as defined in the 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 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. The following medicinal products are approved for the symptomatic therapy of CF:

aztreonam, carbocisteine[2], ceftazidime, ciprofloxacin, colistimethate, dornase alfa, Meronem, 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 basically considered as non-medicinal treatment.

on 3. There are no resolutions for the patient group to be considered in the present therapeutic indication "children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele". For adolescents and adults aged 12 years and older, a resolution dated 18 February 2021 is available for ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor for the present mutation.

[2] Currently off the market

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V". The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

For children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele, there is no specific standard therapy according to the current state of medical knowledge. The above-mentioned medicinal and non-medicinal symptomatic therapy options are available for CF patients aged 6 to 11 years. These are recommended in the present evidence for symptomatic therapy of CF, especially antibiotic therapy of pulmonary infections (ceftazidime, colistimethate, tobramycin), inhaled medicinal products (dornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin), nutritional therapy and support of respiratory function and physiotherapy. Thus, CF treatment is patient-individual in order to alleviate symptoms and improve quality of life in the sense of Best Supportive Care (BSC).

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ivacaftor (IVA) is assessed as follows:

In combination with ivacaftor/ tezacaftor/ elexacaftor (IVA/ TEZ/ ELX), there is indication of a considerable additional benefit in children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele.

Justification:

A multicentre, randomised, double-blind, placebo-controlled phase III VX19-445-116 study (hereafter study 116) was submitted by the pharmaceutical company for the evaluation of the additional benefit of IVA/ TEZ/ ELX + IVA in children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele.

Patients, who were heterozygous for the F508del mutation and carried a minimal function mutation in the CFTR gene on the second allele and had a forced expiratory one second volume (FEV_1%) of ≥ 70% and a lung clearance index ($LCI_{2,5}$) of ≥ 7.5 at the time of screening were enrolled in the study. Patients with acute upper or lower respiratory tract infection or infection of the lungs with organisms associated with a more rapid decline in pulmonary status were excluded from the study. In addition, the basic medication for the treatment of cystic fibrosis should be kept stable within 28 days prior to the start of treatment. A total of 121 patients were enrolled in the study, randomised 1:1 to receive either IVA/ TEZ/ ELX + IVA + BSC (N = 60) or placebo + BSC (N = 61) for 24 weeks.

Furthermore, the pharmaceutical company presents the VX18-445-106 and VX19-445-107 studies as additional evidence. As the two single-arm studies do not allow a comparison with the appropriate comparator therapy, they are not used to derive an additional benefit.

Extent and probability of the additional benefit

Mortality

There were no deaths in the 116 study.

Morbidity

Pulmonary exacerbations

Pulmonary exacerbations, especially those leading to hospitalisation, are a clinically relevant endpoint and should be considered patient-relevant.

The pulmonary exacerbations or severe pulmonary exacerbations were recorded in the 116 study via the AEs or SAEs as "Infectious pulmonary exacerbation of cystic fibrosis" (PT).

For pulmonary exacerbations, there is a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC versus placebo + BSC. For severe pulmonary exacerbations, there is no statistically significant difference between IVA/ TEZ/ ELX + IVA + BSC versus placebo + BSC.

Symptomatology measured via Cystic Fibrosis Questionnaire - Revised (CFQ-R)

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

The endpoint of symptomatology was assessed in the 116 study using the disease-specific, patient-reported CFQ-R (patient version) for the respiratory system and gastrointestinal domains. In addition, these two domains and the weight problems domain were recorded by the parent/ carer version presented additionally.

For the respiratory system and gastrointestinal symptoms domains, the patient version shows a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC versus placebo + BSC.

In addition, the parent/ carer version also shows a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC over placebo + BSC for the domains respiratory system and weight problems and no statistically significant difference between the treatment groups for the domains of gastrointestinal symptoms.

Forced expiratory one second volume (FEV_1%)

Forced one second volume (FEV_1), presented as the percentage of forced one second volume to standardised normal value as FEV_1%, was measured as absolute change over 24 weeks of treatment in the 116 study. There was a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC compared to placebo + BSC.

There are different opinions on the patient relevance of FEV_1%. The overall statement on the extent of the additional benefit remains unaffected.

Lung Clearance Index ($LCI_{2,5}$)

The Lung Clearance Index is a measure for assessing the ventilation inhomogeneity of the lungs and is measured using the gas washout test.

The $LCI_{2,5}$ is considered a surrogate endpoint. Based on the studies submitted by the pharmaceutical company, it cannot be concluded that the $LCI_{2,5}$ is a valid surrogate parameter

for patient-relevant endpoints. However, an influence on the course of the disease can only be measured to a very limited extent in the very young patient population under consideration here, which still has relatively few symptoms. In the written statement procedure, it became clear that the $LCI_{2,5}$ endpoint for detecting early changes in cystic fibrosis is established in clinical practice in this therapeutic indication. Against this background, $LCI_{2,5}$ is used as the relevant endpoint in the age group of patients with cystic fibrosis to be considered here for the benefit assessment. However, due to the lack of long-term data for the $LCI_{2,5}$, the significance of the results with regard to longer-term effects, such as pulmonary exacerbations and improvement of symptomatology, is limited.

The 116 study measured the absolute change in $LCI_{2,5}$ after 24 weeks of treatment compared to the start of the study. There is a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC compared to placebo + BSC.

Body Mass Index (BMI) and BMI z score

BMI is used to assess body weight in relation to height. The body weight or BMI is important in the present indication because developmental disorders and impaired nutrient absorption are among the typical signs of cystic fibrosis. This endpoint is assessed as 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.

In the 116 study, the absolute change in BMI as well as the age-related BMI z score was collected over 24 weeks as the endpoint. For both endpoints, there is a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC versus placebo + BSC.

The included children already had a body weight to height ratio at the start of the study that was within the normal range for the healthy population of the same age and sex (z score). However, it cannot be conclusively assessed to what extent the increasing age and development of the patients influences the outcome.

Sweat chloride concentration

The determination of the sweat chloride concentration is used as standard in the diagnostic process as the values reflect the functionality of the CFTR protein, which is the pathophysiological cause of the disease. The endpoint is not considered directly patient-relevant and is considered additionally as the extent of a reduction in sweat chloride concentration is not directly associated with the extent of change in symptomatology.

The endpoint of sweat chloride concentration was surveyed in the 116 study as absolute change during week 48. There is a statistically significant difference in favour of LUM/ IVA + BSC compared to placebo + BSC.

Quality of life

Health-related quality of life measured via CFQ-R

Health-related quality of life was assessed using the disease-specific, patient-reported CFQ-R (patient version) and includes the domains of physical well-being, emotional state, social limitations, body image, eating disorders and burden of therapy.

In addition, the domains already mentioned (with the exception of the domain of social limitations) as well as the further domains of vitality, school problems and subjective health assessment were recorded by the parent/ carer version presented additionally.

For the domain of social limitations, the patient version shows a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC compared to placebo + BSC.

For the domains of physical well-being, emotional state, body image, eating disorders and burden of therapy, there is no statistically significant difference between the treatment groups for the patient version.

In addition, the parent/ carer version also shows a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC over placebo + BSC for the domain of body image.

Side effects

No effect estimate data are available for the results on the overall rate of adverse events (AEs).

There were no statistically significant differences between the treatment groups for the endpoints of SAEs and discontinuation due to AEs.

For the endpoint of abdominal pain (PT), there is a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC versus placebo + BSC.

In the side effects category, the overall analysis did not show any statistically significant difference between the treatment arms.

Overall assessment

For the benefit assessment of IVA/ TEZ/ ELX + IVA in children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele, the multicentre, randomised, double-blind, placebo-controlled phase III 116 study was submitted compared with the appropriate comparator therapy of best supportive care as determined by the G-BA. The direct comparison leads to results on mortality, morbidity, quality of life and side effects.

There were no deaths in the 116 study.

In the morbidity category, there was a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC versus placebo + BSC for the endpoints of pulmonary exacerbations, $LCI_{2,5}$the BMI and BMI z score, and the respiratory system and gastrointestinal symptoms domains of the patient version of the CFQ-R.

In addition, the additionally presented domains of respiratory system and gastrointestinal symptoms of the parent/ carer version of the CFQ-R as well as FEV_1% and sweat chloride concentration show a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC versus placebo + BSC.

There was no statistically significant difference between the treatment groups for the endpoints of serious pulmonary exacerbations and the additionally presented domain of gastrointestinal symptoms of the parent/ caregiver version of the CFQ-R.

In the category of health-related quality of life, there was a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA + BSC compared to placebo + BSC for the domains of social limitations of the patient version and for the additionally presented domain of body image of the parent/ carer version of the CFQ-R.

For the domains of physical well-being, emotional state, eating disorders and burden of therapy, there was no statistically significant difference between the treatment groups for both versions of the CFQ-R and for the additionally presented domains of the parent/ carer version vitality, school problems and subjective health assessment.

In the side effects category, the overall analysis did not show any statistically significant difference between the treatment arms.

In summary, for children aged 6-11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele, there is a considerable 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 VX19-445-116 study in children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele.

Since the present benefit assessment is based on the results of only one included study, only indications of an additional benefit can be derived with regard to the reliability of data. The risk of bias of all included endpoints with appropriate operationalisation is rated as low. The reliability of data for the additional benefit determined is classified in the category "indication".

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient ivacaftor (invented name: Kalydeco). Kalydeco was approved as an orphan drug but has exceeded the EUR 50 million turnover limit.

The therapeutic indication assessed here is as follows: Kalydeco is indicated in a combination regimen with ivacaftor/ tezacaftor/ elexacaftor (IVA/ TEZ/ ELX + IVA) for the treatment of children aged 6 to 11 years with cystic fibrosis, who are heterozygous for an F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele.

The G-BA determined Best Supportive Care (BSC) to be the appropriate comparator therapy.

For the assessment of the additional benefit, a multicentre, randomised, double-blind, placebo-controlled phase III VX19-445-116 study was submitted by the pharmaceutical company, in which the administration of IVA/ TEZ/ ELX + IVA + BSC was investigated against placebo + BSC in patients in the present therapeutic indication for a duration of 24 weeks.

In the overall assessment of the study results, there is a statistically significant difference in favour of IVA/ TEZ/ ELX + IVA in the endpoints of pulmonary exacerbations, $LCI_{2.5}$, BMI and BMI z score, in the domains of the CFQ-R in the categories of morbidity (respiratory system and gastrointestinal symptoms) and quality of life (social limitations), as well as for the endpoint of abdominal pain (PT).

There were no statistically relevant differences between the treatment groups in the endpoints of mortality, the remaining domains of the CFQ-R, and the overall assessment of the side effects.

The risk of bias of all included endpoints is rated as low, which is why an indication is determined for the reliability of data.

In summary, for children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a minimal function mutation on the second allele, there is an indication of a considerable additional benefit of IVA/ TEZ/ ELX + IVA over the appropriate comparator therapy BSC.

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

In order to ensure consistent consideration of the patient numbers taking into account the most recent resolutions 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 G-BA uses the following derivation of the patient numbers:

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

Altogether, it is assumed that there are currently about 8,000 patients with cystic fibrosis in Germany[3].

This amount differs from the calculation of the pharmaceutical company in the dossier, which assumes 6,340 patients with cystic fibrosis in the total population. However, this figure is subject to uncertainties and is underestimated, as those patients without process data and without a current informed consent form were not taken into account here. In addition, there is currently no evidence that the overall patient population has changed meaningfully since the 2012 reporting volume (8,042 patients ever reported and alive at the time. This figure has already been adjusted for multiple responses according to the information in the report volume.

Therefore, the number of 233 patients in the SHI target population calculated by the pharmaceutical company especially represents an underestimation in the overall assessment.

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: 15 June 2022):

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

Treatment with ivacaftor should only be initiated and monitored by doctors experienced in the therapy of children 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: 15 July 2022).

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 patient-individual 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.

For the cost representation only the dosages of the general case are considered. If the treatment duration is not limited, initial induction schemes are not considered for the cost

[3] Mukoviszidose e.V. – Federal Association for Cystic Fibrosis (CF) Website of Mukoviszidose e.V. [last access 15.06.2022]

representation. Patient-individual dose adjustments (e.g., because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

For dosage depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied. The average body weight of 6-year-olds is 23.6 kg and that of 11-year-olds 42.1 kg. The dosage of ivacaftor/ tezacaftor/ elexacaftor recommended for children varies depending on body weight. According to the product information, children up to a body weight of 30 kg receive 1 x daily 2 tablets of 37.5 mg/ 25 mg/50 mg ivacaftor/ tezacaftor/ elexacaftor and 1 x daily 1 tablet of 75 mg ivacaftor. Above a body weight of 30 kg, children receive 1 x daily 2 tablets of 75 mg/ 50 mg/ 100 mg ivacaftor/ tezacaftor/ elexacaftor and 1 x daily 1 tablet of 150 mg ivacaftor.

Patients in the present therapeutic indication receive the best supportive care. The costs for a best supportive care therapy are different from patient to 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 period:

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 x daily	365	1	365
Ivacaftor/ tezacaftor/ elexacaftor	continuously, 1 x daily	365	1	365
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

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	75 mg - 150 mg	75 mg - 150 mg	1 x 75 mg - 1 x 150 mg	365	365 x 75 mg - 365 x 150 mg
Ivacaftor/ tezacaftor/ elexacaftor	75 mg/ 50 mg/ 100 mg -	75 mg/ 50 mg/ 100 mg -	2 x 37.5 mg/ 25 mg/ 50 mg -	365	730 x 37.5 mg/ 25 mg/ 50 mg -

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	150 mg/ 100 mg/ 200 mg	150 mg/ 100 mg/ 200 mg	2 x 75 mg/ 50 mg/ 100 mg		730 x 75 mg/ 50 mg/ 100 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	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					
Ivacaftor 75 mg	28 FCT	€ 6,751.63	€ 1.77	€ 384.99	€ 6,364.87
Ivacaftor 150 mg	56 FCT	€ 13,492.83	€ 1.77	€ 769.98	€ 12,721.08
Ivacaftor 37.5 mg/ tezacaftor 25 mg/ elexacaftor 50 mg	56 FCT	€ 12,738.95	€ 1.77	€ 726.93	€ 12,010.25
Ivacaftor 75 mg/ tezacaftor 50 mg/ elexacaftor 100 mg	56 FCT	€ 12,738.95	€ 1.77	€ 726.93	€ 12,010.25
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Abbreviations: FCT = film-coated tablets					

LAUER-TAXE® last revised: 15 July 2022

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.

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 11 January 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 3 February 2022, 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 VerfO.

By letter dated 8 February 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 ivacaftor.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 May 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 16 May 2022. The deadline for submitting written statements was 7 June 2022.

The oral hearing was held on 27 June 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 26 July 2022, and the proposed resolution was approved.

At its session on 4 August 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 January 2022	Determination of the appropriate comparator therapy
Working group Section 35a	21 June 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 June 2022	Conduct of the oral hearing,
Working group Section 35a	6 July 2022 20 July 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	26 July 2022	Concluding discussion of the draft resolution
Plenum	4 August 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 August 2022

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

Prof. Hecken