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 (homozygous for F508del 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 homozygous for the F508del mutation in the CTFR gene).

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 homozygous for an F508del mutation in the CFTR gene.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children aged 6 to 11 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene

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

Appropriate comparator therapy for ivacaftor in combination with Ivacaftor/ Tezacaftor/ Elexacaftor:

lumacaftor/ ivacaftor

or

tezacaftor/ ivacaftor in combination with ivacaftor

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 treatment of CF:

CFTR modulators in the following combinations of active ingredients are approved for the patient group to be considered in the present therapeutic indication “patients aged 6 to 11 years with cystic fibrosis who are homozygous for the F508del mutation”: Lumacaftor/ ivacaftor and tezacaftor/ ivacaftor in combination with ivacaftor.

Furthermore, 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. 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

[2] Currently off the market

in the CFTR gene and carry a minimal function mutation on the second allele", resolutions on the combinations of active ingredients lumacaftor/ ivacaftor dated 2 August 2018 and on tezacaftor/ ivacaftor in combination with ivacaftor dated 21 May 2021 are available.

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.

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.

The above medicinal and non-medicinal treatment options are available for children aged 6 to 11 years with cystic fibrosis, who are homozygous for the F508del mutation in the CFTR gene. For patients with CF aged 6 to 11 years, who are homozygous for an F508del mutation, the combinations of active ingredients lumacaftor/ ivacaftor or tezacaftor/ ivacaftor in combination with ivacaftor, which are approved for this mutation, are equally eligible and are therefore determined to be the appropriate comparator therapy.

Patients should also be offered symptomatic therapy, if indicated, with the above medicinal and non-medicinal treatment options. 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, e.g., by physiotherapy.

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 a hint for a non-quantifiable additional benefit in children aged 6 to 11 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene .

Justification:

For the assessment of the additional benefit of IVA/TEZ/ELX + IVA for the treatment of children aged 6 to 11 years with cystic fibrosis, who are homozygous for the F508del mutation in the CFTR gene, the pharmaceutical company submits the single-arm, open-label, phase III VX18-445-106 study (hereafter 106) due to a lack of direct comparator data.

The 106 study enrolled children aged 6 to 11 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene or heterozygous for the F508del mutation in the CFTR gene, have a minimal function mutation on the 2nd allele, and were treated with IVA/ TEZ/ ELX + IVA for different lengths of time, depending on the part of the study (part A: 15

days; part B: 24 weeks). For the early benefit assessment, the pharmaceutical company only considers the sub-population of homozygous children of part B of the study.

In addition, the pharmaceutical company refers to the results of the VX18-445-109 study[3] (hereafter 109 study), which has already been assessed by the G-BA, in patients aged 12 years and older with cystic fibrosis, who are homozygous for the F508del mutation in the CFTR gene, and presents an indirect comparison to the RCT VX19-445-116[4] adjusted for various mutations. Here, the pharmaceutical company assumes transferability of these data for different ages and mutations to the patient population of children aged 6 to 11 years to be considered here.

Furthermore, the pharmaceutical company additionally submits the results of the VX19-445-107 extension study, a non-adjusted, indirect comparison of individual arms of study 106 with IVA/ TEZ/ ELX + IVA to the VX15-661-113, VX13-809-011 and VX14-809-109 studies with the appropriate comparator therapy without a bridge comparator, which, however, cannot be used due to incomplete and insufficiently processed data on the comparability of the patients included in the studies and the results.

Extent and probability of the additional benefit

Mortality

There were no deaths in the 106 study.

Morbidity

Pulmonary exacerbations

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

In the 106 study, there were no pulmonary exacerbations and no hospitalisations due to pulmonary exacerbations.

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 106 study using the disease-specific, patient-reported CFQ-R (patient version) for the respiratory system and gastrointestinal domains. In addition, the parent/ carer version was surveyed.

The evaluation of the domains of the CFQ-R was done in the 106 study as absolute change to week 24.

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

[3] Benefit assessment procedure for the active ingredient ivacaftor/ tezacaftor/ elexacaftor (cystic fibrosis, combination regimen with ivacaftor in patients aged 12 years and older (homozygous for F508del mutation)) https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/584/

[4] Benefit assessment procedure for the active ingredient ivacaftor/ tezacaftor/ elexacaftor (new therapeutic indication: Cystic fibrosis, combination regimen with ivacaftor, from 6 to ≤ 11 years (heterozygous for F508del and MF mutation)) https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/793/

treatment in the 106 study. 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 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 106 study measured the absolute change in $LCI_{2,5}$ after 24 weeks of treatment compared to the start of the study.

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 study 106, the change in BMI as well as the age-related z score from bodyweight to height over 24 weeks was collected as an endpoint.

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.

Study 106 showed a significant reduction in sweat chloride concentration after 24 weeks compared to baseline.

<u>Quality of life</u>

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 parent/ carer version was recorded.

The evaluation of the domains of the CFQ-R was done in the 106 study as absolute change to week 24.

Side effects

In study 106, adverse events (AEs) occurred in all children; severe AEs (grade 3 or 4) were experienced by one patient (3.5%). None of the children experienced serious AEs (SAEs) and none discontinued therapy with IVA/ TEZ/ ELX + IVA due to adverse events.

Evaluation with regard to transfer of additional benefit

Although the above-described study 106 is not suitable for the assessment of the additional benefit compared to the appropriate comparator therapy due to its single-arm design, it provides supporting data for a transfer of the additional benefit.

The European Medicines Agency (EMA) assessment report on IVA/ TEZ/ ELX (Kaftrio)[5] states that the uncontrolled study 106 was used as the basis for extrapolating efficacy data from already approved patient populations (adolescents 12 years and older, adults) to the 6 to 11 year old children who are homozygous for an F508del mutation in the CFTR gene.

The EMA's findings on the medical rationale for transferring data from older patient groups to children aged 6 to 11 years in the same therapeutic indication are also decisive for the G-BA for an evidence transfer.

Cystic fibrosis is an inherited multisystem disease in which mutations in the CFTR gene cause disruptions in the chloride channel of exocrine glands. The pathophysiological background (disturbance in the chloride channel) is thus identical for the patient population of 6 to 11-year-old children relevant here with that of older patients.

Cystic fibrosis is a progressive disease, i.e., the manifestation increases with age, so that younger patients with cystic fibrosis - such as the children under consideration here - still show relatively few symptoms. This means that an influence of the course of the disease on patient-relevant endpoints can only be measured to a limited extent. Thus, symptom burden and improvement of symptoms in the IVA/ TEZ/ ELX + IVA arm is more evident in patients aged 12 years and older compared to children aged 6 to 11 years.

The appropriate comparator therapy defined by the G-BA for patients with cystic fibrosis who are homozygous for an F508del mutation in the CFTR gene is identical for children aged 6 to 11 years as well as for older patients aged 12 years and older (lumacaftor/ ivacaftor or tezacaftor/ ivacaftor in combination with ivacaftor). In this respect, a decisive criterion for evidence transfer in the context of the early benefit assessment is given.

The standards to be applied for the acceptance of evidence-based on a low degree of evidence will also take into account the specificities and limitations of the conduct of paediatric clinical studies.

Considering the fact that there is an identical underlying genetic cause of the disease with comparable pathophysiology, and taking into account the presented data of study 106 in children aged 6 to 11 years, which, compared to the already assessed study 109 indicate largely similar effects in efficacy in patients aged 12 years and older, and in view of the identical appropriate comparator therapy, it is assumed that the positive effects of IVA/ TEZ/ ELX + IVA are transferable.

In study 109, an indication for a considerable additional benefit of IVA/ TEZ/ ELX + IVA over TEZ/ IVA + IVA was derived in elderly patients 12 years and older who are homozygous for the

[5] https://www.ema.europa.eu/en/documents/product-information/kaftrio-epar-product-information_en.pdf

F508del mutation in the CFTR gene. Here, particular attention is paid to the advantages in the endpoints of pulmonary exacerbations, the domains of the CFQ-R on morbidity (respiratory system and weight problems) and the domains of the CFQ-R on health-related quality of life (physical well-being, vitality, role functioning, burden of therapy and subjective health assessment), in which an additional benefit of IVA/ TEZ/ ELX + IVA could be shown compared to the appropriate comparator therapy.

Conclusion

In the overall assessment, the G-BA concludes that the transferability of the additional benefit of IVA/ TEZ/ ELX + IVA from adolescents and adults aged 12 years and older to children aged 6 to 11 years with cystic fibrosis, who are homozygous for the F508del mutation in the CFTR gene, is assumed, especially against the background of the comparable disease pattern, the progressive course of the disease and the limitations in conducting clinical studies in this age group.

Taken together, IVA/ TEZ/ ELX + IVA for the treatment of cystic fibrosis in children aged 6 to 11 years, who are homozygous for the F508del mutation in the CFTR gene, based on the results of the VX19-445-106 study and the results of the VX18-445-109 study in adolescents and adults aged 12 years and older, provides an additional benefit compared with the appropriate comparator therapy, the extent of which cannot be quantified due to the limited evidence available.

Reliability of data (probability of additional benefit)

Due to the uncertainty caused by the transfer of the additional benefit to a younger population, a hint for a non-quantifiable additional benefit can be identified.

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 for the treatment of children aged 6 to 11 years with cystic fibrosis, who are homozygous for an F508del mutation in the CFTR gene.

The G-BA determined the combinations of active ingredients lumacaftor/ ivacaftor and tezacaftor/ ivacaftor in combination with ivacaftor as appropriate comparator therapy.

The pharmaceutical company does not submit any direct comparator studies. It presents the single-arm, open-label, phase III VX18-445-106 study and additionally transfers the results of the VX18-445-109 study, which has already been assessed by the G-BA, in patients aged 12 years and older with cystic fibrosis, who are homozygous for the F508del mutation in the CFTR gene to patients aged 6 to 11 years.

In addition, it presents an unadjusted indirect comparison of individual study arms as well as an indirect comparison adjusted for various mutations, neither of which is suitable for deriving an additional benefit.

Overall, the G-BA concludes that the transferability of the additional benefit of IVA/ TEZ/ ELX + IVA from adolescents aged 12 years and older and adults (resolution of 18 February 2021) to children aged 6 to 11 years with cystic fibrosis, who are homozygous for the F508del mutation in the CFTR gene, is assumed, particularly against the background of the comparable

clinical picture, the progressive course of the disease and the limitations in conducting clinical studies in this age group.

Due to the uncertainty caused by the transfer of the additional benefit to a younger population, a hint for a non-quantifiable additional benefit can be identified.

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[6].

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).

1. The percentage of patients with confirmed homozygous F508del mutation in the CFTR gene is 46.4%[7] (3,712 patients).
2. The percentage of patients aged 6 to < 12 years in the entire patient population is approximately 14.2%[7] (527 patients).
3. Taking into account a proportion of 87.89% of patients insured by the SHI, there are 467 patients in the target population.

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 July 2022):

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

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

[7] Nährlich L, Burkhart M, Wosniok J. German Mucoviscidosis Registry: Report Volume 2018. 2019 https://www.muko.info/fileadmin/user_upload/angebote/qualitaetsmanagement/register/berichtsbaende/berichtsband_2018.pdf [last access 15.06.2022]

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 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.

The dosage of tezacaftor/ ivacaftor recommended for children varies depending on body weight. According to the product information, children up to a body weight of 30 kg receive 1 tablet of tezacaftor 50 mg/ ivacaftor 75 mg 1 x daily and 1 tablet of ivacaftor 75 mg 1 x daily. Above a body weight of 30 kg, children receive 1 tablet of tezacaftor 100 mg/ ivacaftor 150 mg 1 x daily and 1 tablet of ivacaftor 150 mg 1 x daily.

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
Appropriate comparator therapy				
Lumacaftor/ ivacaftor	continuously, 2 x daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Tezacaftor/ ivacaftor	continuously, 1 x daily	365	1	365
Ivacaftor	continuously, 1 x daily	365	1	365

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 - 150 mg/ 100 mg/ 200 mg	75 mg/ 50 mg/ 100 mg - 150 mg/ 100 mg/ 200 mg	2 x 37.5 mg/ 25 mg/ 50 mg - 2 x 75 mg/ 50 mg/ 100 mg	365	730 x 37.5 mg/ 25 mg/ 50 mg - 730 x 75 mg/ 50 mg/ 100 mg
Appropriate comparator therapy					
Lumacaftor/ ivacaftor	200 mg/ 250 mg	400 mg/ 500 mg	4 x 100 mg/ 125 mg	365	1460 x 100 mg/ 125 mg
Tezacaftor/ ivacaftor	50 mg/ 75 mg - 100 mg/ 150 mg	50 mg/ 75 mg - 100 mg/ 150 mg	1 x 50mg/ 75 mg - 1 x 100 mg/ 150 mg	365	365 x 50mg/ 75 mg - 365 x 100 mg/ 150 mg
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

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
Appropriate comparator therapy					
Lumacaftor/ ivacaftor	112 FCT	€ 12,076.43	€ 1.77	€ 689.09	€ 11,385.57
Tezacaftor 50 mg/ ivacaftor 75 mg	28 FCT	€ 5,292.45	€ 1.77	€ 301.66	€ 4,989.02
Tezacaftor 100 mg/ ivacaftor 150 mg	28 FCT	€ 5,292.45	€ 1.77	€ 301.66	€ 4,989.02
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
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