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/ tezacaftor/ elexacaftor (new therapeutic indication: cystic fibrosis, combination regimen with ivacaftor, 2 to ≤ 5 years (homozygous for F508del mutation))

of 16 May 2024

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 combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor (Kaftrio) was listed for the first time on 1 September 2020 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

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Kaftrio 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 turnover of ivacaftor/ tezacaftor/ elexacaftor with the statutory health insurance at pharmacy sales prices, including value-added tax exceeded € 30 million; therefore, evidence must be provided for ivacaftor/ tezacaftor/ elexacaftor in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit, compared with the appropriate comparator therapy must be demonstrated.

On 22 November 2023, ivacaftor/ tezacaftor/ elexacaftor 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 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 from 12.12.2008, sentence 7).

On [date], the pharmaceutical company has 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 combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor with the new therapeutic indication "Treatment of cystic fibrosis (CF) in paediatric patients aged 2 to ≤ 5 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene" 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 dossier assessment. The benefit assessment was published on 1 March 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of ivacaftor/ tezacaftor/ elexacaftor compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well as of the addendum drawn up by the IQWiG on the benefit assessment. 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/ tezacaftor/ elexacaftor.

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/ tezacaftor/ elexacaftor (Kaftrio) in accordance with the product information

Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

Therapeutic indication of the resolution (resolution of 16.05.2024):

Ivacaftor/ tezacaftor/ elexacaftor is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis in paediatric patients aged 2 to ≤ 5 years who are homozygous for the F508del mutation in the CFTR gene.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children aged 2 to ≤ 5 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene

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

- Lumacaftor/ ivacaftor

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or

3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. The following medicinal products are approved for the treatment of CF:

The CFTR modulator lumacaftor/ ivacaftor is approved for the patient group to be considered in the present therapeutic indication "patients aged 2 to ≤ 5 years with cystic fibrosis who are homozygous for the F508del mutation".

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. A resolution on the combination of active ingredients lumacaftor/ ivacaftor from 2 August 2018 is available for the patient group to be considered in this therapeutic indication. For the combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor, a resolution for adults and adolescents aged 12 years and older from 18 February 2021 and a resolution for children aged 6 to < 12 years from 4 August 2022 are available for this 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 2 to ≤ 5 years with cystic fibrosis, who are homozygous for the F508del mutation in the CFTR gene. For patients with CF aged 2 to ≤ 5 years, who are homozygous for an F508del mutation, the combination of active ingredients lumacaftor/ ivacaftor approved for this mutation are eligible and is 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.

[2] Currently off the market

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ivacaftor/ tezacaftor/ elexacaftor is assessed as follows:

In combination with ivacaftor, there is a hint for a non-quantifiable additional benefit in children aged 2 to ≤ 5 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 2 to ≤ 5 years with cystic fibrosis, who are homozygous for the F508del mutation in the CFTR gene, the pharmaceutical company submits the results of the single-arm phase III VX20-445-111 study (hereafter 111) due to a lack of direct comparator data.

In addition, the pharmaceutical company subsequently submitted information on the potential transfer of evidence as part of the written and oral statement procedure.

The 111 study enrolled children aged 2 to ≤ 5 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. Only homozygous patients were included in the present assessment.

Extent and probability of the additional benefit

Mortality

There were no deaths in the 111 study.

Morbidity

Pulmonary exacerbations

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

In study 111, 6 pulmonary exacerbations as well as one hospitalisation due to pulmonary exacerbation and one pulmonary exacerbation requiring treatment with IV antibiotics occurred in a total of 23 study participants.

Ratio of body weight to body height, z-score

In study 111, the change in z-score from bodyweight to height over 24 weeks was collected, among others, as an endpoint. The ratio of bodyweight to body size is important for the present indication, since developmental disorders and impaired nutrient absorption are among the typical signs of cystic fibrosis. This endpoint is considered to be a patient-relevant

morbidity parameter, especially in children and infants with characteristic, disease-related growth disturbances. Data adjusted for age and sex (z-scores) are preferred over absolute values. The enrolled infants 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). At the end of the study, there were no changes in the ratio of body weight to height at baseline. 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 111 showed a significant reduction in sweat chloride concentration after 24 weeks compared to baseline.

Quality of life

Endpoints in the health-related quality of life category were not examined in study 111.

Side effects

In study 111, adverse events (AEs) occurred in all 23 children. No serious AEs or severe AEs (grade 3 or 4) occurred and no patients discontinued treatment with IVA/TEZ/ELX due to adverse events.

Assessment with regard to transfer of additional benefit

Although the above-described study 111 is unsuitable 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)[3] states that the uncontrolled study 111 was used as the basis for extrapolating efficacy data from already approved older patient populations to the 2 to ≤ 5-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 2 to ≤ 5 years in the same therapeutic indication are also decisive for the G-BA for transfer of evidence.

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 2 to ≤ 5-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

[3] European Medicines Agency. Kaftrio; SmPC [online]. 2024 [accessed: 26.04.2024]. URL: https://www.ema.europa.eu/en/documents/product-information/kaftrio-epar-product-information_en.pdf

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 arm is more evident in patients aged 12 years and older compared to children aged 2 to ≤ 5 and 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 covered in the resolutions on IVA/TEZ/ELX for children aged 2 to ≤ 5 years and 6 to ≤ 11 years as well as for older patients aged 12 years and over by the combination of active ingredients lumacaftor/ ivacaftor (the combination of active ingredients tezacaftor/ ivacaftor is also approved for patients aged 6 years and over). In this respect, a decisive criterion for transfer of evidence 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 111 in children aged 2 to ≤ 5 years, which, compared to the already assessed studies in children aged 6 to ≤ 11 years (VX18-445-106 study) as well as in patients aged 12 years and older (VX18-445-109 study) indicate largely similar effects in efficacy, and in view of the identical appropriate comparator therapy, it is assumed that the positive effects of IVA/TEZ/ELX are transferable.

In subjects aged 12 years and older[4] in the present therapeutic indication, an indication of a major additional benefit of IVA/TEZ/ELX compared with lumacaftor/ ivacaftor was identified, among other things due to a benefit in the patient-relevant endpoint of pulmonary exacerbations and improvements in health-related quality of life. For children aged 6 to ≤ 11 years[5] in the present therapeutic indication, a hint for a non-quantifiable additional benefit of IVA/TEZ/ELX was identified.

Conclusion

In the overall assessment, the G-BA concludes that the transferability of the additional benefit of IVA/TEZ/ELX from older patients to children aged 2 to ≤ 5 years with cystic fibrosis, who are homozygous for the F508del mutation in the CFTR gene, is assumed, especially 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.

Taken together, an additional benefit compared with the appropriate comparator therapy results for IVA/TEZ/ELX for the treatment of cystic fibrosis in children aged 2 to ≤ 5 years who are homozygous for the F508del mutation in the CFTR gene, based on the results of the VX20-445-111 study and the results of the studies in older subjects with the same mutation (6 to ≤

[4] Benefit assessment procedure for the combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor (exceeding € 50 million limit, cystic fibrosis, combination regimen with ivacaftor in patients aged 12 years and older (homozygous for F508del mutation)); URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/584/

[5] Benefit assessment procedure for the combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor (new therapeutic indication: cystic fibrosis, combination regimen with ivacaftor, 6 to 11 years (homozygous for F508del mutation)); URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/801/

11 years: VX18-445-106 study, 12 years and older: VX18-445-109); the extent of this additional benefit is non-quantifiable 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 combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor. Ivacaftor/ tezacaftor/ elexacaftor (invented name: Kaftrio) was approved as an orphan drug but has exceeded the EUR 30 million turnover limit.

The present resolution refers to the therapeutic indication "combination regimen with ivacaftor for the treatment of cystic fibrosis in paediatric patients aged 2 to ≤ 5 years who are homozygous for the F508del mutation in the CFTR gene".

The G-BA determined the combination of active ingredients lumacaftor/ ivacaftor as an appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company presented the single-arm, open-label phase III VX20-445-111 study and additionally transferred the results of the studies on ivacaftor/ tezacaftor/ elexacaftor in older subjects with cystic fibrosis and the same mutation (VX18-445-106 study in children aged 6 to ≤ 11 years and VX18-445-109 study in patients aged 12 years and older) to children aged 2 to ≤ 5 years; these results had already been assessed by the G-BA.

Based on these studies, the G-BA derived a hint for a non-quantifiable additional benefit in children aged 6 to ≤ 11 years and an indication of a major additional benefit in adults and adolescents aged 12 years and older, in each case compared to lumacaftor/ ivacaftor.

Particularly against the background of the comparable clinical picture, the progressive course of the disease and the limitations in the conduct of the clinical studies, the G-BA concludes that the transferability of the additional benefit of ivacaftor/ tezacaftor/ elexacaftor from older patients to the 2 to ≤ 5-year-old children to be considered here is assumed. 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].

[6] Mukoviszidose e.V. – Bundesverband Cystische Fibrose (CF) Website of Mukoviszidose e.V. [last access 08.04.2024]

This amount differs from the calculation of the pharmaceutical company in the dossier, which assumes 6,973 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 249 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 Kaftrio (active ingredient: ivacaftor/ tezacaftor/ elexacaftor) at the following publicly accessible link (last access: 7 May 2024):

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

Treatment with ivacaftor/ tezacaftor/ elexacaftor should only be initiated and monitored by doctors experienced in treating cystic fibrosis.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

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

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

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 2-year-olds is 14.1 kg and that of 5-year-olds 20.8 kg. According to the product information, children weighing 14 kg or more receive 1 sachet of granules of 75 mg/50 mg/100 mg Ivacaftor/ tezacaftor/ elexacaftor once daily in the morning and 1 sachet of granules of ivacaftor 75 mg once daily in the evening.

According to the product information, children aged 2 to 5 years and weighing 14 kg or more receive lumacaftor/ ivacaftor 2 x daily, 1 sachet of granules each 150 mg/ 188 mg lumacaftor/ ivacaftor.

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/ tezacaftor/ elexacaftor	Continuously, 1 x daily	365.0	1	365.0
Ivacaftor	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Lumacaftor/ ivacaftor	Continuously, 2 x daily	365.0	1	365.0

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/ tezacaftor/ elexacaftor	75 mg/ 50 mg/ 100 mg	75 mg/ 50 mg/ 100 mg	1 x 75 mg/ 50 mg/ 100 mg	365.0	365.0 x 75 mg/50 mg /100 mg
Ivacaftor	75 mg	75 mg	1 x 75 mg	365.0	365.0 x 75
Appropriate comparator therapy					
Lumacaftor/ ivacaftor	150 mg/188 mg	300 mg/376 mg	2 x 150 mg/188 mg	365.0	730.0 x 150 mg/188 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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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/ tezacaftor 50 mg/ elexacaftor 100 mg	28 GRA	€ 10,795.42	€ 2.00	€ 615.93	€ 10,177.49
Ivacaftor 75 mg	56 GRA	€ 12,054.53	€ 2.00	€ 687.84	€ 11,364.69
Appropriate comparator therapy					
Lumacaftor 150 mg/ ivacaftor 188 mg	56 GRA	€ 12,025.12	€ 2.00	€ 686.16	€ 11,336.96
Abbreviations: GRA = granules					

LAUER-TAXE® last revised: 15 April 2024

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 need to be taken into account.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit

had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Children aged 2 to ≤ 5 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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 28 November 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 1 December 2023, the pharmaceutical company submitted a dossier for the benefit assessment of ivacaftor/ tezacaftor/ elexacaftor to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 5 December 2023, 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 combination of active ingredients ivacaftor/ tezacaftor/ elexacaftor.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 March 2024. The deadline for submitting statements was 22 March 2024.

The oral hearing was held on 8 April 2024.

By letter dated 12 April 2024, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 26 April 2024.

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 7 May 2024, and the proposed resolution was approved.

At its session on 16 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 November 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	3 April 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	8 April 2024	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 April 2024 29 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	7 May 2024	Concluding discussion of the draft resolution
Plenum	16 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 May 2024

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

Prof. Hecken