

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,
from 2 to \leq 5 years (heterozygous for F508del and RF
mutation))

of 16 May 2024

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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.

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 sales volume of ivacaftor/ tezacaftor/ elexacaftor with the statutory health insurance at pharmacy sales prices, including value-added tax exceeded € 30 million. Evidence must therefore 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 1 December 2023, 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 decision 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. 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 Methods¹ 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 heterozygous for an F508del mutation in the CFTR gene and carry a residual function mutation on the second allele.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Children aged 2 to ≤ 5 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a residual 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 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. No medicinal products are approved for the causal treatment of CF in this therapeutic indication. The following medicinal products are approved for the symptomatic therapy of CF: aztreonam, carbocisteine², 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 on the early benefit assessment for the patient group to be considered in the present therapeutic indication "children aged 2 to ≤ 5 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a residual function mutation on the second allele". 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 systematic 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 2 to ≤ 5 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a residual 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 2 to ≤ 5 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 Currently off the market

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, an additional benefit is not proven in children aged 2 to ≤ 5 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a residual function mutation on the second allele.

Justification:

The pharmaceutical company did not submit any direct comparator studies versus the appropriate comparator therapy for the assessment of the additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor in children aged 2 to ≤ 5 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a residual function mutation on the second allele.

A transfer of the additional benefit on the basis of the information provided by the pharmaceutical company is neither possible from patients with a deviating mutation type nor from older patients to the population in the present therapeutic indication.

For the transfer of the additional benefit between different mutation types, the pharmaceutical company argues purely qualitatively about the mode of action of the intervention and does not present any data on patient-relevant endpoints for the patients relevant in the present research question. Furthermore, the pharmaceutical company's argumentation for the transfer of additional benefit between different mutation types is based on the results of the label-enabling, single-arm VX20-445-111 study and the associated VX20-445-112 extension study as well as the VX17-445-102 (RCT), VX19-445-116 (RCT) and VX18-445-106 (single-arm) studies, which enrolled patients of different age groups with F508del mutation and minimal function mutation and for whom a different appropriate comparator therapy was defined.

The significant VX18-445-104 study, which the pharmaceutical company uses for its argumentation for the transfer of the additional benefit of patients aged 12 years and older, was already assessed as being unsuitable in the context of the benefit assessments for this age group due to a too short study duration, and the additional benefit was assessed as not proven for this age group.

An additional benefit of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor compared with the appropriate comparator therapy is therefore not proven in the present therapeutic indication.

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 heterozygous for an F508del mutation in the CFTR gene and carry a residual function mutation on the second allele".

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

For the benefit assessment of ivacaftor/ tezacaftor/ elexacaftor in combination with ivacaftor, no direct comparator studies versus the appropriate comparator therapy were presented in the present therapeutic indication.

A transfer of the additional benefit on the basis of the information provided by the pharmaceutical company is neither possible from patients with a deviating mutation type nor from older patients to the population in the present therapeutic indication.

In the overall assessment, an additional benefit is not proven for children aged 2 to ≤ 5 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a residual function mutation on the second allele.

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 Germany³.

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 20 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

³ [Mukoviszidose e.V. – Bundesverband Cystische Fibrose \(CF\)](#) Website of Mukoviszidose e.V. [last access 08.04.2024]

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.

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/ tezacaftor/ elexacaftor | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| Ivacaftor | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| 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/ 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 |
| 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. 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 |
| Best supportive care | Different from patient to patient | | | | |
| Appropriate comparator therapy | | | | | |
| Best supportive care | Different from patient to patient | | | | |
| 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 heterozygous for the F508del mutation in the CFTR gene and carry a residual function mutation on the second allele

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.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 28 November 2023.

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 23 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.

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, |
| 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